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(54) **Title:** METHODS USING SUBSTITUTED HYDROXYPROLINE DERIVATIVES FOR KILLING NEMATODES AND NEMATODE EGGS

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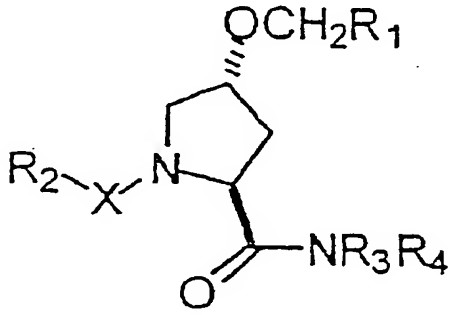

(47)

(57) **Abstract:** Methods and compositions for the control of nematodes are disclosed. Specifically, substituted hydroxyproline anthelmintic compounds of formula (47) have been found to advantageously control nematodes at concentrations which are non-phytotoxic. The anthelmintic compounds can be used in conjunction with other nematicidal agents such as free fatty acids, fatty acid salts, avermectins, ivermectin, and milbemycin. R_1 is C_{1-5} branched or straight alkyl (optionally substituted with phenyl); C_{3-8} cyclic alkyl; aryl (optionally substituted with C_{1-10} branched or straight alkyl, or OC_{1-5}); R_2 is C_{1-5} branched or straight alkyl which is optionally substituted with aryl (optionally substituted OC_{1-5} or OAr); NCH_2R_5 wherein R_5 is Ar (optionally substituted with OCF_3); OC_{1-5},CH_2OR_6 wherein R_6 is C_{1-5} alkyl or C_{3-8} cyclic alkyl (optionally substituted with C_{1-5} straight or branched alkyl, or OC_{1-5}); aryl (optionally substituted with C_{1-5} straight or branched alkyl; OC_{1-5}; halogen; naphthyl (optionally substituted with OC_{1-5} or an amine); or a 3 ring fused polycyclic group; R_3 is H; C_{1-5} branched or straight alkyl whhich is optionally substituted with aryl (optionally substituted with halogen, OC_{1-5}, C_{1-5} branched or straight alkyl); OC_{1-5}; C_{2-8} ether; cyclic alkyl (optionally substituted with C_{1-10} branched, straight, or cyclic alkyl); aryl (optionally substituted with halogen, C_{1-5} straight or branched alkyl; OCF_3); R_4 is H, C_{1-5} branched or straight alkyl which is optionally substituted with aryl (optionally substituted with halogen, OC_{1-5}, C_{1-5} branched or straight alkyl; OC_{1-5}; C_{2-8} ether; cyclic alkyl (optionally substituted with C_{1-10} branched, straight, or cyclic alkyl); aryl (optionally substituted with halogen, C_{1-5} straight or branched alkyl; OCF_3); and X is CO or SO_2.

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DESCRIPTION

METHODS AND MATERIALS FOR KILLING NEMATODES AND NEMATODE EGGS

Cross-Reference to a Related Application

This application claims the benefit of U.S. Provisional Application No. 60/179,005, filed January 28, 2000.

Background of the Invention

Nematodes are important plant pests which cause millions of dollars of damage each year to turf grasses, ornamental plants, and food crops. Efforts to eliminate or minimize damage caused by nematodes in agricultural settings have typically involved the use of soil fumigation with materials such as chloropicrin, methyl bromide, and dazomet, which volatilize to spread the active ingredient throughout the soil. Such fumigation materials can be highly toxic and may create an environmental hazard. Various non-fumigant chemicals have also been used, but these, too, create serious environmental problems and can be highly toxic to humans.

The accepted methodology for control of nematodes afflicting animals has centered around the use of the drug benzimidazole and its congeners. The use of these drugs on a wide scale has led to many instances of resistance among nematode populations (Prichard, R.K. *et al.* [1980] "The problem of anthelmintic resistance in nematodes," *Austr. Vet. J.* 56:239-251; Coles, G.C. [1986] "Anthelmintic resistance in sheep," In *Veterinary Clinics of North America: Food Animal Practice*, Vol 2:423-432 [Herd, R.P., Eds.] W.B. Saunders, New York).

The pesticidal activity of avermectins is well known. The avermectins are disaccharide derivatives of pentacyclic, 16-membered lactones. They can be divided into four major compounds: A_{1a}, A_{2a}, B_{1a}, and B_{2a}; and four minor compounds: A_{1b}, A_{2b}, B_{1b}, and B_{2b}.

The organism which produces avermectins was isolated and identified as *Streptomyces avermitilis* MA-4680 (NRRL-8165). Characteristics of the avermectin producing culture and the fermentation process are well documented and known to those

skilled in the art (Burg, R.W. *et al.* [1979] "Avermectins, New Family of Potent Anthelmintic Agents: Producing Organism and Fermentation," *Antimicrob. Agents Chemother.* 15(3):361-367). The isolation and purification of these compounds is also described in U.S. Patent No. 4,310,519 issued January 12, 1982.

Another family of pesticides produced by fermentation are the milbemycins, which are closely related to the avermectins. The milbemycins can be produced by a variety of *Streptomyces* and originally differed from the avermectins only in the C-13 position. The milbemycins and their many derivatives are also well known to those skilled in the art and are the subject of U.S. patents. See, for example, U.S. Patent No. 4,547,520.

While the avermectins were initially investigated for their anthelmintic activities, they were later found to have other insecticidal properties, although the degree varies. The activity of avermectins must generally be determined empirically.

22,23-dihydroavermectin B_1 is a synthetic derivative of the avermectins and has been assigned the nonproprietary name of ivermectin. It is a mixture of 80% 22,23-dihydroavermectin B_{1a} and 20% 22,23-dihydroavermectin B_{1b}. Ivermectin has been tested on a variety of laboratory and domestic animals for control of nematodes, ticks, and heartworms.

Avermectin B_{2a} is active against the root-knot nematode, *Meloidogyne incognita*. It is reported to be 10-30 times as potent as commercial contact nematicides when incorporated into soil at 0.16-0.25 kg/ha (Boyce Thompson Institute for Plant Research 58th Annual Report [1981]; Putter, I. *et al.* [1981] "Avermectins: Novel Insecticides, Acaracides, and Nematicides from a Soil Microorganism," *Experientia* 37:963-964). Avermectin B_{2a} is not toxic to tomatoes or cucumbers at rates of up to 10 kg/ha. Avermectin B_1 is a combination of avermectin B_{1a} (major component) and avermectin B_{1b}. It has demonstrated a broad spectrum of insecticidal activities. The data indicate that avermectin B_1 is primarily a miticide, although it is also effective on the Colorado potato beetle, potato tuberworm, beet armyworm, diamondback moth, gypsy moth, and the European corn borer.

The use of avermectins in various agricultural applications has been described in publications and patents. The use of avermectin with spray oils (lightweight oil compositions) has been described. See, for example, U.S. Patent No. 4,560,677 issued

December 24, 1985; EPO applications 0 094 779 and 0 125 155; and Anderson, T.E., J.R. Babu, R.A. Dybas, H. Mehta (1986) *J. Econ. Entomol.* 79:197-201.

There is a continuing need for new, alternative materials and methods useful for killing nematodes.

Brief Summary of the Invention

The subject invention concerns substituted compositions and processes for controlling nematodes. In one embodiment, the subject invention comprises the use of certain substituted hydroxyproline compounds to control nematodes which infest and afflict animals. Nematodes which infest plants or the situs of plants can also be controlled using the methods and compositions of the subject invention, as can other acarid and arthropod pests.

Preferred compounds useful according to the subject invention can be represented by the Formulae I, II, III, IV, and V as further described herein.

1. A urea derivative of the following Formula I:

$$Ar\text{-}(Alk)_{0-1}\text{-}NH\text{-}CO\text{-}NR^1\text{-}Alk\text{-}R^2 \qquad \text{(Formula I)}$$

wherein Ar is aryl or heteroaryl optionally substituted by one or more R^3 groups;

each Alk is a linear or cyclic alkylene radical of up to 8 C atoms;

R^1 is H or C_{1-6} alkyl;

R^2 is heteroaryl or heterocycloalkyl optionally substituted by Ar, or forms such a group by cyclisation with R^1; and

R^3 is OH, halogen, CF_3, OCF, or a group selected from NH_2, SO_2-C_{1-6} alkyl, C_{6-10} aryl,

C_{6-10} aryloaxy, C_{5-6} cycloalkyl, C_{1-5} alkoxy, and C_{1-6} alkyl, said group being optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} alkyl, phenyl, halogen, or CF_3.

Particularly preferred anthelmintic compounds according to Formula I are exemplified herein by compounds represented by structures 1-10 (depicted in Figures 1-10, respectively), which have been assigned the respective reference numbers:

AKC 111 (STRUCTURE 1),

AKC 112 (STRUCTURE 2),

AKC 113 (STRUCTURE 3),

AKC 107 (STRUCTURE 4),

AKC 114 (STRUCTURE 5),
AKC 108 (STRUCTURE 6),
AKC 115 (STRUCTURE 7),
AKC 116 (STRUCTURE 8),
AKC 117 (STRUCTURE 9), and
AKC 118 (STRUCTURE 10).

2. A heterocycle-substituted amide of the following Formula II:

$$Ar\text{-}(Alk)_{0\text{-}1}\text{-}NH\text{-}CO\text{-}Het \qquad \text{(Formula II)}$$

wherein Ar is aryl or heteroaryl optionally substituted by one or more R^3 groups;

each Alk is an optionally cyclic alkylene radical of up to 8 C atoms;

Het is heteroaryl or heterocycloalkyl optionally substituted by Ar and/or R^3; and

R^3 is OH, halogen, CF_3, OCF_3, or a group selected from NH_2, SO_2 alkyl, $C_{6\text{-}10}$ aryl, $C_{1\text{-}6}$ alkoxy, and $C_{1\text{-}6}$ alkyl, said group being optionally substituted by OH, $C_{1\text{-}6}$ alkoxy, $C_{1\text{-}6}$ alkyl, phenyl, halogen, or CF_3.

Particularly preferred anthelmintic compounds according to Formula II are exemplified herein by compounds represented by structures 11-25 (depicted in Figures 11-25 respectively), which have been assigned the respective reference numbers:

AKC 119 (STRUCTURE 11),
AKC 110 (STRUCTURE 12),
AKC 120 (STRUCTURE 13),
AKC 121 (STRUCTURE 14),
AKC 2153 (STRUCTURE 15),
AKC 122 (STRUCTURE 16),
AKC 104 (STRUCTURE 17),
AKC 123 (STRUCTURE 18),
AKC 124 (STRUCTURE 19),
AKC 125 (STRUCTURE 20),
AKC 105 (STRUCTURE 21),
AKC 126 (STRUCTURE 22),
AKC 102 (STRUCTURE 23),
AKC 103 (STRUCTURE 24), and

AKC 171 (STRUCTURE 25).

3. A secondary arylamine of the following Formula III:

Ar-NH-CHR-CH_2-CO-Y (Formula III)

wherein Ar is aryl or heteroaryl optionally substituted by one or more R^3 groups ;

R is aryl, heteroaryl, or heterocycloalkyl optionally substituted by R^3 ;

Y is C_{1-6} alkyl, aryl, or heteroaryl optionally substituted by R^3 ;

or R and Y together form a cycloalkyl or heterocycloalkyl ring; and

R^3 is OH, halogen, CF_3, OCF_3, or a group selected from NH_2, SO_2 alkyl, C_{6-10} aryl, C_{1-6} alkoxy, and C_{1-6} alkyl, said group being optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} alkyl, phenyl, halogen, or CF_3.

Particularly preferred anthelmintic compounds according to Formula III are exemplified herein by compounds represented by structures 26-31 (depicted in Figures 26-31, respectively), which have been assigned the respective reference numbers:

AKC 128 (STRUCTURE 26),

AKC 129 (STRUCTURE 27),

AKC 130 (STRUCTURE 28),

AKC 131 (STRUCTURE 29),

AKC 132 (STRUCTURE 30), and

AKC 133 (STRUCTURE 31).

4. A diaryl amine of the following Formula IV:

Ar-$(Z)_{0-1}$-Ar-$(CH_2)_{0-1}$-NHR (Formula IV)

wherein Ar is aryl or heteroaryl optionally substituted by one or more R^3 groups;

Z is NH, O, S, or Alk; and Alk is a linear or cyclic alkylene radical of up to 8 C atoms

wherein said radical optionally includes one or more heteroatoms;

R is H or R^3,

R^3 is OH, halogen, CF_3, OCF_3, or a group selected from NH_2, SO_2 alkyl, C_{6-10} aryl, C_{1-6} alkoxy, and C_{1-6} alkyl, said group being optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} alkyl, phenyl, halogen, or CF_3.

Particularly preferred anthelmintic compounds according to Formula IV are exemplified by compounds represented by structures 32-37 (depicted in Figures 32-37, respectively), which have been assigned the respective reference numbers:

AKC 109 (STRUCTURE 32),
AKC 134 (STRUCTURE 33),
AKC 135 (STRUCTURE 34),
AKC 136 (STRUCTURE 35),
AKC 137 (STRUCTURE 36), and
AKC 138 (STRUCTURE 37).

5. A substituted heteropolycyclic compound of the following Formula V:

$$Het_2\text{-}Q \qquad \text{(Formula V)}$$

wherein Het_2 is two or three fused aromatic rings including one or more heteroatoms selected from N, O and S, and Q includes at least one substituent selected from OH, $COOR^3$ and $CONHR^3$, and optionally also another substituent selected from alkyl and alkenyl of up to 10 C atoms;

wherein R^3 is OH, halogen, CF_3, OCF_3, or a group selected from NH_2, SO_2 alkyl, C_{6-10} aryl, C_{1-6} alkoxy, and C_{1-6} alkyl, said group being optionally substituted by OH, C_{1-6} alkoxy, C_{1-6} alkyl, phenyl, halogen, or CF_3.

Particularly preferred anthelmintic compounds according to Formula V are exemplified by compounds represented by structures 38-43 (depicted in Figures 38-43, respectively), which have been assigned the respective reference numbers:

AKC 139 (STRUCTURE 38),
AKC 140 (STRUCTURE 39),
AKC 141 (STRUCTURE 40),
AKC 142 (STRUCTURE 41),
AKC 143 (STRUCTURE 42), and
AKC 144 (STRUCTURE 43).

For the foregoing Formulae I, II, III, IV, and V, as well as throughout this disclosure, the following definitions apply.

"Aryl" refers to an aromatic group, typically of 6-10 C atoms, such as phenyl or naphthyl.

"Alk" includes, for example, $(CH_2)_n$ wherein n is an integer of up to 6, *e.g.* 1, 2, 3, or 4, or cyclohexylene.

"Heteroaryl" means an aromatic group including one or more heteroatoms selected from O, S and N. It will typically have 5 or 6 ring atoms. It may also be fused to one or more aryl groups. Examples are in the illustrated compounds.

"Heterocycloalkyl" means a cycloalkyl group in which one or more C atoms are replaced by one or more heteroatoms selected from O, S and N. It will typically have 5 or 6 ring atoms. Examples are in the illustrated compounds of structures 1-43.

Other preferred anthelmintic compounds useful according to the subject invention are represented by structures 44, 45, and 46 (depicted in Figures 44-46, respectively), and have been assigned the respective reference numbers:

AKC 145 (STRUCTURE 44),

AKC 146 (STRUCTURE 45), and

AKC 147 (STRUCTURE 46).

The invention process is particularly valuable to control nematodes which are pests to animals, as well as nematodes attacking the roots of desired crop plants, ornamental plants, and turf grasses. The desired crop plants can be, for example, cotton, soybean, tomatoes, potatoes, grapes, strawberries, bananas, or vegetables.

In one embodiment of the subject invention, the subject anthelmintic compounds are used in conjunction with one or more other nematicidal agents. The other nematicidal agents may be, for example, a biological agent, an avermectin, a milbemycin, or a fatty acid.

In another embodiment, the subject invention further provides methods for killing the eggs of nematodes. Thus, the subject invention further relates to the surprising discovery that certain compounds have ovicidal activity against nematode eggs. Compositions comprising the anthelmintic compounds of the subject invention are particularly useful for preplant applications in nematode-control schemes.

Description of the Drawings

Figure 1 depicts Structure 1 which represents anthelmintic compound AKC 111.

Figure 2 depicts Structure 2 which represents anthelmintic compound AKC 112.

Figure 3 depicts Structure 3 which represents anthelmintic compound AKC 113.

Figure 4 depicts Structure 4 which represents anthelmintic compound AKC 107.

Figure 5 depicts Structure 5 which represents anthelmintic compound AKC 114.

Figure 6 depicts Structure 6 which represents anthelmintic compound AKC 108.

Figure 7 depicts Structure 7 which represents anthelmintic compound AKC 115.

Figure 8 depicts Structure 8 which represents anthelmintic compound AKC 116.

Figure 9 depicts Structure 9 which represents anthelmintic compound AKC 117.

Figure 10 depicts Structure 10 which represents anthelmintic compound AKC 118.

Figure 11 depicts Structure 11 which represents anthelmintic compound AKC 119.

Figure 12 depicts Structure 12 which represents anthelmintic compound AKC 110.

Figure 13 depicts Structure 13 which represents anthelmintic compound AKC 120.

Figure 14 depicts Structure 14 which represents anthelmintic compound AKC 121.

Figure 15 depicts Structure 15 which represents anthelmintic compound AKC 2153.

Figure 16 depicts Structure 16 which represents anthelmintic compound AKC 122.

Figure 17 depicts Structure 17 which represents anthelmintic compound AKC 104.

Figure 18 depicts Structure 18 which represents anthelmintic compound AKC 123.

Figure 19 depicts Structure 19 which represents anthelmintic compound AKC 124.

Figure 20 depicts Structure 20 which represents anthelmintic compound AKC 125.

Figure 21 depicts Structure 21 which represents anthelmintic compound AKC 105.

Figure 22 depicts Structure 22 which represents anthelmintic compound AKC 126.

Figure 23 depicts Structure 23 which represents anthelmintic compound AKC 102.

Figure 24 depicts Structure 24 which represents anthelmintic compound AKC 103.

Figure 25 depicts Structure 25 which represents anthelmintic compound AKC 171.

Figure 26 depicts Structure 26 which represents anthelmintic compound AKC 128.

Figure 27 depicts Structure 27 which represents anthelmintic compound AKC 129.

Figure 28 depicts Structure 28 which represents anthelmintic compound AKC 130.

Figure 29 depicts Structure 29 which represents anthelmintic compound AKC 121.

Figure 30 depicts Structure 30 which represents anthelmintic compound AKC 132.

Figure 31 depicts Structure 31 which represents anthelmintic compound AKC 133.

Figure 32 depicts Structure 32 which represents anthelmintic compound AKC 109.

Figure 33 depicts Structure 33 which represents anthelmintic compound AKC 134.

Figure 34 depicts Structure 34 which represents anthelmintic compound AKC 135.

Figure 35 depicts Structure 35 which represents anthelmintic compound AKC 136.

Figure 36 depicts Structure 36 which represents anthelmintic compound AKC 137.

Figure 37 depicts Structure 37 which represents anthelmintic compound AKC 138.

Figure 38 depicts Structure 38 which represents anthelmintic compound AKC 139.

Figure 39 depicts Structure 39 which represents anthelmintic compound AKC 140.

Figure 40 depicts Structure 40 which represents anthelmintic compound AKC 141.

Figure 41 depicts Structure 41 which represents anthelmintic compound AKC 142.

Figure 42 depicts Structure 42 which represents anthelmintic compound AKC 143.

Figure 43 depicts Structure 43 which represents anthelmintic compound AKC 144.

Figure 44 depicts Structure 44 which represents anthelmintic compound AKC 145.

Figure 45 depicts Structure 45 which represents anthelmintic compound AKC 146.

Figure 46 depicts Structure 46 which represents anthelmintic compound AKC 147.

Figure 47 depicts a basic structure, Structure 47, of a preferred class of anthelmintic compound.

Figure 48 depicts anthelmintic compound AKC 1297 of the class represented in Figure 47.

Figure 49 depicts anthelmintic compound AKC 1299 of the class represented in Figure 47.

Figure 50 depicts anthelmintic compound AKC 1300 of the class represented in Figure 47.

Figure 51 depicts anthelmintic compound AKC 1298 of the class represented in Figure 47.

Figure 52 depicts anthelmintic compound AKC 1301 of the class represented in Figure 47.

Figure 53 depicts anthelmintic compound AKC 1302 of the class represented in Figure 47.

Figure 54 depicts anthelmintic compound AKC 126 of the class represented in Figure 47.

Figure 55 depicts anthelmintic compound AKC 1303 of the class represented in Figure 47.

Figure 56 depicts anthelmintic compound AKC 1314 of the class represented in Figure 47.

Figure 57 depicts anthelmintic compound AKC 1305 of the class represented in Figure 47.

Figure 58 depicts anthelmintic compound AKC 1315 of the class represented in Figure 47.

Figure 59 depicts anthelmintic compound AKC 1306 of the class represented in Figure 47.

Figure 60 depicts anthelmintic compound AKC 1316 of the class represented in Figure 47.

Figure 61 depicts anthelmintic compound AKC 1307 of the class represented in Figure 47.

Figure 62 depicts anthelmintic compound AKC 1317 of the class represented in Figure 47.

Figure 63 depicts anthelmintic compound AKC 1308 of the class represented in Figure 47.

Figure 64 depicts anthelmintic compound AKC 1318 of the class represented in Figure 47.

Figure 65 depicts anthelmintic compound AKC 1304 of the class represented in Figure 47.

Figure 66 depicts anthelmintic compound AKC 1309 of the class represented in Figure 47.

Figure 67 depicts anthelmintic compound AKC 102 of the class represented in Figure 47.

Figure 68 depicts anthelmintic compound AKC 1313 of the class represented in Figure 47.

Figure 69 depicts anthelmintic compound AKC 1319 of the class represented in Figure 47.

Figure 70 depicts anthelmintic compound AKC 1310 of the class represented in Figure 47.

Figure 71 depicts anthelmintic compound AKC 1320 of the class represented in Figure 47.

Figure 72 depicts anthelmintic compound AKC 1311 of the class represented in Figure 47.

Figure 73 depicts anthelmintic compound AKC 1321 of the class represented in Figure 47.

Figure 74 depicts anthelmintic compound AKC 1312 of the class represented in Figure 47.

Figure 75 depicts anthelmintic compound AKC 1322 of the class represented in Figure 47.

Figure 76 depicts anthelmintic compound AKC 1323 of the class represented in Figure 47.

Figure 77 depicts anthelmintic compound AKC 1326 of the class represented in Figure 47.

Figure 78 depicts anthelmintic compound AKC 1324 of the class represented in Figure 47.

Figure 79 depicts anthelmintic compound AKC 1327 of the class represented in Figure 47.

Figure 80 depicts anthelmintic compound AKC 1325 of the class represented in Figure 47.

Figure 81 depicts anthelmintic compound AKC 1328 of the class represented in Figure 47.

Figure 82 depicts anthelmintic compound AKC 1331 of the class represented in Figure 47.

Figure 83 depicts anthelmintic compound AKC 1329 of the class represented in Figure 47.

Figure 84 depicts anthelmintic compound AKC 1330 of the class represented in Figure 47.

Figure 85 depicts anthelmintic compound AKC 1332 of the class represented in Figure 47.

Figure 86 depicts anthelmintic compound AKC 1333 of the class represented in Figure 47.

Figure 87 depicts anthelmintic compound AKC 1334 of the class represented in Figure 47.

Figure 88 depicts anthelmintic compound AKC 1335 of the class represented in Figure 47.

Figure 89 depicts anthelmintic compound AKC 1337 of the class represented in Figure 47.

Figure 90 depicts anthelmintic compound AKC 1336 of the class represented in Figure 47.

Figure 91 depicts anthelmintic compound AKC 1339 of the class represented in Figure 47.

Figure 92 depicts anthelmintic compound AKC 1345 of the class represented in Figure 47.

Figure 93 depicts anthelmintic compound AKC 1340 of the class represented in Figure 47.

Figure 94 depicts anthelmintic compound AKC 1346 of the class represented in Figure 47.

Figure 95 depicts anthelmintic compound AKC 1338 of the class represented in Figure 47.

Figure 96 depicts anthelmintic compound AKC 1341 of the class represented in Figure 47.

Figure 97 depicts anthelmintic compound AKC 1342 of the class represented in Figure 47.

Figure 98 depicts anthelmintic compound AKC 1347 of the class represented in Figure 47.

Figure 99 depicts anthelmintic compound AKC 1343 of the class represented in Figure 47.

Figure 100 depicts anthelmintic compound AKC 1348 of the class represented in Figure 47.

Figure 101 depicts anthelmintic compound AKC 1344 of the class represented in Figure 47.

Figure 102 depicts anthelmintic compound AKC 1349 of the class represented in Figure 47.

Figure 103 depicts anthelmintic compound AKC 1353 of the class represented in Figure 47.

Figure 104 depicts anthelmintic compound AKC 1350 of the class represented in Figure 47.

Figure 105 depicts anthelmintic compound AKC 1351 of the class represented in Figure 47.

Figure 106 depicts anthelmintic compound AKC 1352 of the class represented in Figure 47.

Figure 107 depicts anthelmintic compound AKC 1354 of the class represented in Figure 47.

Figure 108 depicts anthelmintic compound AKC 1355 of the class represented in Figure 47.

Figure 109 depicts anthelmintic compound AKC 1356 of the class represented in Figure 47.

Figure 110 depicts anthelmintic compound AKC 1357 of the class represented in Figure 47.

Figure 111 depicts anthelmintic compound AKC 1358 of the class represented in Figure 47.

Figure 112 depicts anthelmintic compound AKC 1359 of the class represented in Figure 47.

Figure 113 depicts anthelmintic compound AKC 1360 of the class represented in Figure 47.

Figure 114 depicts anthelmintic compound AKC 1368 of the class represented in Figure 47.

Figure 115 depicts anthelmintic compound AKC 1361 of the class represented in Figure 47.

Figure 116 depicts anthelmintic compound AKC 1369 of the class represented in Figure 47.

Figure 117 depicts anthelmintic compound AKC 1362 of the class represented in Figure 47.

Figure 118 depicts anthelmintic compound AKC 1363 of the class represented in Figure 47.

Figure 119 depicts anthelmintic compound AKC 1364 of the class represented in Figure 47.

Figure 120 depicts anthelmintic compound AKC 1365 of the class represented in Figure 47.

Figure 121 depicts anthelmintic compound AKC 1366 of the class represented in Figure 47.

Figure 122 depicts anthelmintic compound AKC 1367 of the class represented in Figure 47.

Figure 123 depicts anthelmintic compound AKC 1377 of the class represented in Figure 47.

Figure 124 depicts anthelmintic compound AKC 1370 of the class represented in Figure 47.

Figure 125 depicts anthelmintic compound AKC 1378 of the class represented in Figure 47.

Figure 126 depicts anthelmintic compound AKC 1371 of the class represented in Figure 47.

Figure 127 depicts anthelmintic compound AKC 1372 of the class represented in Figure 47.

Figure 128 depicts anthelmintic compound AKC 1379 of the class represented in Figure 47.

Figure 129 depicts anthelmintic compound AKC 1373 of the class represented in Figure 47.

Figure 130 depicts anthelmintic compound AKC 1380 of the class represented in Figure 47.

Figure 131 depicts anthelmintic compound AKC 1374 of the class represented in Figure 47.

Figure 132 depicts anthelmintic compound AKC 1375 of the class represented in Figure 47.

Figure 133 depicts anthelmintic compound AKC 1381 of the class represented in Figure 47.

Figure 134 depicts anthelmintic compound AKC 1376 of the class represented in Figure 47.

Figure 135 depicts anthelmintic compound AKC 1382 of the class represented in Figure 47.

Figure 136 depicts anthelmintic compound AKC 1390 of the class represented in Figure 47.

Figure 137 depicts anthelmintic compound AKC 1383 of the class represented in Figure 47.

Figure 138 depicts anthelmintic compound AKC 1384 of the class represented in Figure 47.

Figure 139 depicts anthelmintic compound AKC 1391 of the class represented in Figure 47.

Figure 140 depicts anthelmintic compound AKC 1385 of the class represented in Figure 47.

Figure 141 depicts anthelmintic compound AKC 1392 of the class represented in Figure 47.

Figure 142 depicts anthelmintic compound AKC 1386 of the class represented in Figure 47.

Figure 143 depicts anthelmintic compound AKC 1393 of the class represented in Figure 47.

Figure 144 depicts anthelmintic compound AKC 1387 of the class represented in Figure 47.

Figure 145 depicts anthelmintic compound AKC 1388 of the class represented in Figure 47.

Figure 146 depicts anthelmintic compound AKC 1394 of the class represented in Figure 47.

Figure 147 depicts anthelmintic compound AKC 1389 of the class represented in Figure 47.

Figure 148 depicts anthelmintic compound AKC 1395 of the class represented in Figure 47.

Figure 149 depicts anthelmintic compound AKC 1396 of the class represented in Figure 47.

Figure 150 depicts anthelmintic compound AKC 1397 of the class represented in Figure 47.

Figure 151 depicts anthelmintic compound AKC 1259 of the class represented in Figure 47.

Figure 152 depicts anthelmintic compound AKC 1260 of the class represented in Figure 47.

Figure 153 depicts anthelmintic compound AKC 1261 of the class represented in Figure 47.

Figure 154 depicts anthelmintic compound AKC 1262 of the class represented in Figure 47.

Figure 155 depicts anthelmintic compound AKC 1268 of the class represented in Figure 47.

Figure 156 depicts anthelmintic compound AKC 1263 of the class represented in Figure 47.

Figure 157 depicts anthelmintic compound AKC 1267 of the class represented in Figure 47.

Figure 158 depicts anthelmintic compound AKC 1269 of the class represented in Figure 47.

Figure 159 depicts anthelmintic compound AKC 1264 of the class represented in Figure 47.

Figure 160 depicts anthelmintic compound AKC 1270 of the class represented in Figure 47.

Figure 161 depicts anthelmintic compound AKC 1265 of the class represented in Figure 47.

Figure 162 depicts anthelmintic compound AKC 1271 of the class represented in Figure 47.

Figure 163 depicts anthelmintic compound AKC 1266 of the class represented in Figure 47.

Figure 164 depicts anthelmintic compound AKC 1406 of the class represented in Figure 47.

Figure 165 depicts anthelmintic compound AKC 1398 of the class represented in Figure 47.

Figure 166 depicts anthelmintic compound AKC 1407 of the class represented in Figure 47.

Figure 167 depicts anthelmintic compound AKC 1399 of the class represented in Figure 47.

Figure 168 depicts anthelmintic compound AKC 1408 of the class represented in Figure 47.

Figure 169 depicts anthelmintic compound AKC 1400 of the class represented in Figure 47.

Figure 170 depicts anthelmintic compound AKC 1409 of the class represented in Figure 47.

Figure 171 depicts anthelmintic compound AKC 1401 of the class represented in Figure 47.

Figure 172 depicts anthelmintic compound AKC 1410 of the class represented in Figure 47.

Figure 173 depicts anthelmintic compound AKC 1402 of the class represented in Figure 47.

Figure 174 depicts anthelmintic compound AKC 1411 of the class represented in Figure 47.

Figure 175 depicts anthelmintic compound AKC 1403 of the class represented in Figure 47.

Figure 176 depicts anthelmintic compound AKC 1412 of the class represented in Figure 47.

Figure 177 depicts anthelmintic compound AKC 1404 of the class represented in Figure 47.

Figure 178 depicts anthelmintic compound AKC 1413 of the class represented in Figure 47.

Figure 179 depicts anthelmintic compound AKC 1405 of the class represented in Figure 47.

Figure 180 depicts anthelmintic compound AKC 1422 of the class represented in Figure 47.

Figure 181 depicts anthelmintic compound AKC 1414 of the class represented in Figure 47.

Figure 182 depicts anthelmintic compound AKC 1423 of the class represented in Figure 47.

Figure 183 depicts anthelmintic compound AKC 1415 of the class represented in Figure 47.

Figure 184 depicts anthelmintic compound AKC 1424 of the class represented in Figure 47.

Figure 185 depicts anthelmintic compound AKC 1416 of the class represented in Figure 47.

Figure 186 depicts anthelmintic compound AKC 1425 of the class represented in Figure 47.

Figure 187 depicts anthelmintic compound AKC 1417 of the class represented in Figure 47.

Figure 188 depicts anthelmintic compound AKC 1418 of the class represented in Figure 47.

Figure 189 depicts anthelmintic compound AKC 1426 of the class represented in Figure 47.

Figure 190 depicts anthelmintic compound AKC 1419 of the class represented in Figure 47.

Figure 191 depicts anthelmintic compound AKC 1427 of the class represented in Figure 47.

Figure 192 depicts anthelmintic compound AKC 1420 of the class represented in Figure 47.

Figure 193 depicts anthelmintic compound AKC 1428 of the class represented in Figure 47.

Figure 194 depicts anthelmintic compound AKC 1421 of the class represented in Figure 47.

Figure 195 depicts anthelmintic compound AKC 1437 of the class represented in Figure 47.

Figure 196 depicts anthelmintic compound AKC 1429 of the class represented in Figure 47.

Figure 197 depicts anthelmintic compound AKC 1438 of the class represented in Figure 47.

Figure 198 depicts anthelmintic compound AKC 1430 of the class represented in Figure 47.

Figure 199 depicts anthelmintic compound AKC 1439 of the class represented in Figure 47.

Figure 200 depicts anthelmintic compound AKC 1431 of the class represented in Figure 47.

Figure 201 depicts anthelmintic compound AKC 1440 of the class represented in Figure 47.

Figure 202 depicts anthelmintic compound AKC 1432 of the class represented in Figure 47.

Figure 203 depicts anthelmintic compound AKC 1441 of the class represented in Figure 47.

Figure 204 depicts anthelmintic compound AKC 1433 of the class represented in Figure 47.

Figure 205 depicts anthelmintic compound AKC 1442 of the class represented in Figure 47.

Figure 206 depicts anthelmintic compound AKC 1434 of the class represented in Figure 47.

Figure 207 depicts anthelmintic compound AKC 1443 of the class represented in Figure 47.

Figure 208 depicts anthelmintic compound AKC 1435 of the class represented in Figure 47.

Figure 209 depicts anthelmintic compound AKC 1444 of the class represented in Figure 47.

Figure 210 depicts anthelmintic compound AKC 1436 of the class represented in Figure 47.

Figure 211 depicts anthelmintic compound AKC 1445 of the class represented in Figure 47.

Figure 212 depicts anthelmintic compound AKC 1446 of the class represented in Figure 47.

Figure 213 depicts anthelmintic compound AKC 1272 of the class represented in Figure 47.

Figure 214 depicts anthelmintic compound AKC 1273 of the class represented in Figure 47.

Figure 215 depicts anthelmintic compound AKC 1274 of the class represented in Figure 47.

Figure 216 depicts anthelmintic compound AKC 1275 of the class represented in Figure 47.

Figure 217 depicts anthelmintic compound AKC 1276 of the class represented in Figure 47.

Figure 218 depicts anthelmintic compound AKC 1280 of the class represented in Figure 47.

Figure 219 depicts anthelmintic compound AKC 1277 of the class represented in Figure 47.

Figure 220 depicts anthelmintic compound AKC 1278 of the class represented in Figure 47.

Figure 221 depicts anthelmintic compound AKC 1279 of the class represented in Figure 47.

Figure 222 depicts anthelmintic compound AKC 1455 of the class represented in Figure 47.

Figure 223 depicts anthelmintic compound AKC 1447 of the class represented in Figure 47.

Figure 224 depicts anthelmintic compound AKC 1456 of the class represented in Figure 47.

Figure 225 depicts anthelmintic compound AKC 1457 of the class represented in Figure 47.

Figure 226 depicts anthelmintic compound AKC 1448 of the class represented in Figure 47.

Figure 227 depicts anthelmintic compound AKC 1458 of the class represented in Figure 47.

Figure 228 depicts anthelmintic compound AKC 1449 of the class represented in Figure 47.

Figure 229 depicts anthelmintic compound AKC 1459 of the class represented in Figure 47.

Figure 230 depicts anthelmintic compound AKC 1450 of the class represented in Figure 47.

Figure 231 depicts anthelmintic compound AKC 1454 of the class represented in Figure 47.

Figure 232 depicts anthelmintic compound AKC 1460 of the class represented in Figure 47.

Figure 233 depicts anthelmintic compound AKC 1451 of the class represented in Figure 47.

Figure 234 depicts anthelmintic compound AKC 1461 of the class represented in Figure 47.

Figure 235 depicts anthelmintic compound AKC 1452 of the class represented in Figure 47.

Figure 236 depicts anthelmintic compound AKC 1453 of the class represented in Figure 47.

Figure 237 depicts anthelmintic compound AKC 1469 of the class represented in Figure 47.

Figure 238 depicts anthelmintic compound AKC 1462 of the class represented in Figure 47.

Figure 239 depicts anthelmintic compound AKC 1470 of the class represented in Figure 47.

Figure 240 depicts anthelmintic compound AKC 1463 of the class represented in Figure 47.

Figure 241 depicts anthelmintic compound AKC 1471 of the class represented in Figure 47.

Figure 242 depicts anthelmintic compound AKC 1464 of the class represented in Figure 47.

Figure 243 depicts anthelmintic compound AKC 1472 of the class represented in Figure 47.

Figure 244 depicts anthelmintic compound AKC 1465 of the class represented in Figure 47.

Figure 245 depicts anthelmintic compound AKC 1466 of the class represented in Figure 47.

Figure 246 depicts anthelmintic compound AKC 1473 of the class represented in Figure 47.

Figure 247 depicts anthelmintic compound AKC 1467 of the class represented in Figure 47.

Figure 248 depicts anthelmintic compound AKC 1474 of the class represented in Figure 47.

Figure 249 depicts anthelmintic compound AKC 1468 of the class represented in Figure 47.

Figure 250 depicts anthelmintic compound AKC 1475 of the class represented in Figure 47.

Figure 251 depicts anthelmintic compound AKC 1486 of the class represented in Figure 47.

Figure 252 depicts anthelmintic compound AKC 1478 of the class represented in Figure 47.

Figure 253 depicts anthelmintic compound AKC 1487 of the class represented in Figure 47.

Figure 254 depicts anthelmintic compound AKC 1479 of the class represented in Figure 47.

Figure 255 depicts anthelmintic compound AKC 1488 of the class represented in Figure 47.

Figure 256 depicts anthelmintic compound AKC 1480 of the class represented in Figure 47.

Figure 257 depicts anthelmintic compound AKC 1489 of the class represented in Figure 47.

Figure 258 depicts anthelmintic compound AKC 1476 of the class represented in Figure 47.

Figure 259 depicts anthelmintic compound AKC 1477 of the class represented in Figure 47.

Figure 260 depicts anthelmintic compound AKC 1481 of the class represented in Figure 47.

Figure 261 depicts anthelmintic compound AKC 1490 of the class represented in Figure 47.

Figure 262 depicts anthelmintic compound AKC 1482 of the class represented in Figure 47.

Figure 263 depicts anthelmintic compound AKC 1491 of the class represented in Figure 47.

Figure 264 depicts anthelmintic compound AKC 1483 of the class represented in Figure 47.

Figure 265 depicts anthelmintic compound AKC 1492 of the class represented in Figure 47.

Figure 266 depicts anthelmintic compound AKC 1484 of the class represented in Figure 47.

Figure 267 depicts anthelmintic compound AKC 1493 of the class represented in Figure 47.

Figure 268 depicts anthelmintic compound AKC 1485 of the class represented in Figure 47.

Figure 269 depicts anthelmintic compound AKC 1494 of the class represented in Figure 47.

Figure 270 depicts anthelmintic compound AKC 1495 of the class represented in Figure 47.

Figure 271 depicts anthelmintic compound AKC 1496 of the class represented in Figure 47.

Figure 272 depicts anthelmintic compound AKC 1497 of the class represented in Figure 47.

Figure 273 depicts anthelmintic compound AKC 1281 of the class represented in Figure 47.

Figure 274 depicts anthelmintic compound AKC 1282 of the class represented in Figure 47.

Figure 275 depicts anthelmintic compound AKC 1283 of the class represented in Figure 47.

Figure 276 depicts anthelmintic compound AKC 1289 of the class represented in Figure 47.

Figure 277 depicts anthelmintic compound AKC 1284 of the class represented in Figure 47.

Figure 278 depicts anthelmintic compound AKC 1290 of the class represented in Figure 47.

Figure 279 depicts anthelmintic compound AKC 1285 of the class represented in Figure 47.

Figure 280 depicts anthelmintic compound AKC 1286 of the class represented in Figure 47.

Figure 281 depicts anthelmintic compound AKC 1287 of the class represented in Figure 47.

Figure 282 depicts anthelmintic compound AKC 1291 of the class represented in Figure 47.

Figure 283 depicts anthelmintic compound AKC 1288 of the class represented in Figure 47.

Figure 284 depicts anthelmintic compound AKC 1498 of the class represented in Figure 47.

Figure 285 depicts anthelmintic compound AKC 1499 of the class represented in Figure 47.

Figure 286 depicts anthelmintic compound AKC 1292 of the class represented in Figure 47.

Figure 287 depicts anthelmintic compound AKC 1296 of the class represented in Figure 47.

Figure 288 depicts anthelmintic compound AKC 1293 of the class represented in Figure 47.

Figure 289 depicts anthelmintic compound AKC 1294 of the class represented in Figure 47.

Figure 290 depicts anthelmintic compound AKC 1295 of the class represented in Figure 47.

Figure 291 depicts one library scheme by which the skilled artisan can create the compounds represented by the structure depicted in Figure 47.

Figure 292 depicts Scaffold 1.

Figure 293 depicts Scaffold 2.

Figure 294 depicts Scaffold 3.

Figure 295 depicts Scaffold 4.

Figure 296 depicts Scaffold 5.

Figure 297 depicts Scaffold 6.

Figure 298 depicts a preferred pathway for synthesis of hydroxyproline derivatives.

Figure 299 depicts a preferred alternate pathway for synthesis of hydroxyproline derivatives.

Figure 300 depicts a synthetic pathway using diamines on nitrophenol carbonate linker.

Figure 301 compares the original base structure of intended compounds with the preferred base structure of the subject compounds.

Detailed Disclosure of the Invention

The process of the subject invention concerns the use of certain organic compounds to control the infestation of plants or animals by nematodes. These organic compounds comprise Formulae I, II, III, IV, and V, as well as Structures 44, 45, and 46. In a particularly preferred embodiment of the subject invention, the anthelmintic compound is selected from the group consisting of Compounds 1-46 represented by Structures 1-46. Particularly preferred are the compounds represented by Structures 22 and 23, and compounds related thereto as represented by Structure 47 depicted in Figure 47, and as further exemplified by Structures 48-290 depicted in Figures 48 through 290. Preferred anthelmintic compounds useful in accord with the subject invention are represented by Structure 47, wherein:

R_1 is C_{1-5} branched or straight alkyl (optionally substituted with phenyl); C_{3-8} cyclic alkyl; aryl (optionally substituted with C_{1-10} branched or straight alkyl, or OC_{1-5});

R_2 is C_{1-5} branched or straight alkyl which is optionally substituted with aryl (optionally substituted with OC_{1-5} or OAr); NCH_2R_5 wherein R_5 is Ar (optionally substituted with OCF_3); OC_{1-5}; CH_2OR_6 wherein R_6 is C_{1-5} alkyl or C_{3-8} cyclic alkyl (optionally substituted with C_{1-5} straight or branched alkyl, or OC_{1-5}); aryl (optionally substituted with C_{1-5} straight or branched alkyl; OC_{1-5}; halogen; naphthyl (optionally substituted with OC_{1-5} or an amine); or a 3 ring fused polycyclic group;

R_3 is H; C_{1-5} branched or straight alkyl which is optionally substituted with aryl (optionally substituted with halogen, OC_{1-5}, C_{1-5} branched or straight alkyl); OC_{1-5}; C_{2-8} ether; cyclic alkyl (optionally substituted with C_{1-10} branched, straight, or cylcic alkyl); aryl (optionally substituted with halogen, C_{1-5} straight or branched alkyl, OCF_3);

R_4 is H; C_{1-5} branched or straight alkyl which is optionally substituted with aryl (optionally substituted with halogen, OC_{1-5}, C_{1-5} branched or straight alkyl); OC_{1-5}; C_{2-8} ether; cyclic alkyl (optionally substituted with C_{1-10} branched, straight, or cylcic alkyl); aryl (optionally substituted with halogen, C_{1-5} straight or branched alkyl, OCF_3); and

X is CO or SO_2.

Generally, the anthelmintic compounds of the subject invention can be unsubstituted or substituted, saturated or unsaturated. The anthelmintic component of an anthelmintic compounds used according to the subject invention may be a single anthelmintic compound or a mixture of two or more anthelmintic compounds. The subject compounds may be used in conjunction with other anthelmintic compounds, including the free acids and salts of the anthelmintic compounds of the present invention. The salts may be, for example, sodium or potassium salts, or ammonium salts. As would be apparent to the ordinary skilled artisan, physiologically acceptable acids and salts of the subject anthelmintic compounds can readily be made and used in accord with the teachings herein, and are hereby expressly included by reference to each compound or group of compounds. For example, "AKC 1297", "Compound 48", or "Structure 48" each refer to the same compounds and each is intended to include the physiologically acceptable acids and salts thereof. In addition, the subject anthelmintic compounds may have an assymetrical carbon atom, *i.e.*, optically active site. These compounds exist in (R) and (S) enantiomeric forms. Both the (R) and (S) enantiomers of the subject compounds are contemplated by the subject invention.

Anthelmintic compounds specifically exemplified herein include Compounds 1-46 represented by Structures 1-46 above, and Compounds 48-290 represented by Structures 48-290 depicted in Figures 48-290.

The subject compounds used in the invention can be applied to animals, the living and feeding areas of animals, plants, or to the situs of plants needing nematode control. The anthelmintic compositions may be applied by, for example, drip and drench techniques. With the drip application, the subject compositions can be applied directly

to the base of plants or to the soil root zone. The composition may be applied through already existing drip irrigation systems. This procedure is particularly applicable for ornamental plants, strawberries, tomatoes, potatoes, grapes, and vegetables. Alternatively, a drench application can be used. For treating plants, a sufficient quantity of the anthelmintic composition is applied such that the composition drains to the root area of the plants. An important aspect of the subject invention is the surprising discovery that certain compounds have excellent nematicidal activity at concentrations which are not phytotoxic.

The drench technique can be used for a variety of crops and for turf grasses. The drench technique can also be used for animals. Preferably, for administration to animals the anthelmintic composition would be administered orally to facilitate activity against internal nematode parasites. The compositions of the subject invention can readily be applied using the teachings provided herein.

In a preferred embodiment of the subject invention, an anthelmintic compound will be applied as an aqueous microemulsion. As described herein, the concentration of the active ingredient should be sufficient to control the nematode infestation without causing phytotoxicity to the desired plants. The concentration of anthelmintic compound may be, for example, from about 0.0001% to about 2%, preferably from about 0.025% to about 1%, and, most preferably, from about 0.05% to about 0.5%.

The anthelmintic composition used according to the subject invention can be applied in conjunction with one or more other nematicidal agents. The other nematicidal agent may, for example, be applied simultaneously or sequentially with the anthelmintic. Such other nematicidal agents include, for example, avermectins, the *B.t.*s, and fatty acids.

The avermectin compound used according to the subject invention may be any of the avermectins, milbemycins, or derivatives of either, having activity against nematodes. The avermectin's activity will be enhanced when combined with an anthelmintic compound as described herein. Thus, the specific combination of ingredients can be manipulated to provide the optimal composition for a particular application.

Standard concentrations of avermectins are well known to those skilled in the art. For example, the avermectin compounds can be employed in the combination of the

subject invention at concentrations of from about 0.03 to about 110 parts per million (ppm). Preferably, from about 1 to about 5 ppm are employed.

As would be readily appreciated by a person skilled in the art, the delivery of the subject anthelmintic and/or avermectin compound can be calculated in terms of the active ingredient applied per unit area. For example, the subject anthelmintic may be applied at a rate of about 0.02 lb/acre to about 0.1 lb/acre and, preferably, from about 0.5 lb/acre to about 2 lbs/acre. Similarly, the avermectin product can be applied at a rate of up to about 16 oz. of formulated product ("AVID," available from Merck) per acre. Preferably, about 4 oz. to about 8 oz. formulated "AVID" per acre would be used. Thus, the avermectin compound can be applied up to about 0.02 lb/acre. Preferably, the rate of avermectin is between about 0.005 lb/acre and 0.01 lb/acre. A person of ordinary skill in the art would readily appreciate that the desired application rate of the active ingredients could be achieved using a great variety of different concentrations of active ingredients while varying the application rate of the solution. Thus, a large quantity of dilute solution could be applied or a smaller quantity of a more concentrated solution.

A variety of different avermectins or related compounds can be used according to the subject invention. Ivermectin may also be used according to the subject invention, as may the milbemycins. For brevity, the term "avermectin" is used herein to refer to all the avermectins and their derivatives as well as related compounds such as the milbemycins and the ivermectins. "Derivatives" refer to chemical modifications of the avermectins or milbemycins which are well known and available to those skilled in this art. Such derivatives are described, for example, in U.S. Patent No. 4,560,677. Avermectin is readily available under a variety of tradenames including "AVID," "ZEPHYR," "VERTIMEC," and "AGRI-MEK."

The anthelmintic compositions of the subject invention may also be used in conjunction with nematicidal agents other than the avermectins. For example, the anthelmintic compounds may be used with biological agents such as *Bacillus thuringiensis* or with nematicidal fungi. In this context, the anthelmintic composition could be applied at concentrations which would not antagonize the action of the biological agent. The biologically active agent may be in a live proliferative form or may be in a dead stabilized form as described, for example, in U.S. Patent Nos. 4,695,462 and 4,695,455. Furthermore, the anthelmintic compositions of the subject invention may be

used with plants which are specifically bred or engineered for nematode resistance. The plants may, for example, be transformed with *B.t.* genes which confer nematode resistance or may simply be hybrids or varieties selected for such resistance. The anthelmintic compositions of the subject invention are particularly effective against free-living ectoparasitic nematodes and, therefore, combined use with plants selected for endoparasitic nematode resistance is highly advantageous.

The subject invention further relates to the surprising discovery that the anthelmintics of the subject invention have ovicidal activity against nematode eggs. Thus, in another embodiment, provided are methods for killing the eggs of nematodes, including those within cysts or egg masses that are commonly formed by *Heterodera, Globodera*, and *Meloidogyne* (cyst and root-knot) species.

The ovicidal compositions according to the subject invention are particularly useful for preplant applications in nematode-control schemes. In addition, the ovicidal compositions of the subject invention can be advantageously used as postplant nematicides, especially because of their relatively low phytotoxicity. In the latter embodiments, ovicidal compositions of the subject invention can be delivered, after planting and at appropriate, essentially non-phytotoxic concentrations of anthelmintic compounds, along with irrigation water and/or plant nutrients to ensure a continuous zone of nematode protection to the enlarging plant root mass. Thus, when applied using these techniques, which include drench or drip systems as are known in the art, phytopathogenic nematodes in their vermiform (wormlike) and egg stages are controlled.

Anthelmintic compounds having Formulae I, II, III, IV, and V, Structure 47, and most preferably Structures 1-46, and particularly Structures 22, 23 and Structures 48-290, are used in preferred embodiments for killing nematode eggs. In addition, microemulsions of the subject compounds are highly preferred for ovicidal applications. In preferred embodiments, the anthelmintic compound(s) will be present in a concentration of greater than about 150 ppm. More preferably, the concentration will be greater than about 200 ppm; most preferably it will be about 250 ppm or more. For certain conditions, the anthelmintic compounds should be applied at high concentrations of about 1,000 ppm to about 5,000 ppm or more.

In light of the subject disclosure, one skilled in the art could readily use a variety of application techniques and formulations to prevent the hatching of nematode eggs in a variety of agricultural, farm-related, and garden-related settings.

Examples of animal parasitic nematodes against which the subject compounds can be used include the following:

Amblyomma spp.
Babesia spp. (RBC)
Bunostomum spp.
Calliphorid larvae
Capillaria spp.
Chabertia ovina
Chorioptes
Cooperia spp.
Cryptosporidium sp.
Damalinia ovis
Damalinia caprae
Demodex
Dermacentor spp.
Dicrocoelium dentriticum
Dictyocaulus filaria
Echinococcus hydatid cyst
Eimeria spp.
Elaeophora schneideri
Fasciola hepatica
Fasciola gigantica
Fascioloides magna
Giardia sp.
Gongylonema spp.
Haematobia irritans
Haemonchus contortus contortus
Ixodes
Linguatula serrata larvae
Linguatula serrata nymphs
Linognathus spp.
M. domestica
Marshallagia marshalli
Melophagus ovinus
Moniezia benedeni
Moniezia expansa
Muellerius capillaris
Musca autumnalis
Nematodirus spp.
Oesophagostomum spp.
Oestrus ovis

Ornithodoros
Ostertagia circumcincta
Ostertagia trifurcata
Otobius
Paramphistomum sp.
Parelaphostrongylus tenuis
Protostrongylus sp.
Psoroptes
Rhipicephalus spp.
Sarcoptes scabiei
Sarcocystis spp.
Sarcocystis spp. cysts
Schistosoma spp.
Stomoxys calcitrans
Strongyloides papillosus
Taenia hydatigena cysticerci
Taenia multiceps coenurus
Taenia ovis cysticerci
Thelazia
Thysanosoma actinoides
Theileria spp.C)
Toxocara vitulorum
Toxoplasma gondii
Toxoplasma gondii cysts
Trichostrongylus axei
Trichostrongylus spp.
Trichuris ovis
Trypanosoma spp. (plasma)

It has been found that helminth, acarid and arthropod endo- and ectoparasitic infestations may be controlled, prevented or eliminated, by applying to, injecting or orally dosing said animals with an endo- or ectoparasiticidally effective amount of the subject anthelmintic compounds, preferably the above-described Structure 1-46 compounds. This may be achieved by applying the compound to the skin, hide and/or hair of the animals, or injecting or orally dosing said animals with a solid or liquid formulated composition.

For control of flea infestations, treatment of the infested animal to control adults in conjunction with treatment of the area occupied by the infested animal to control flea larvae is recommended. The compositions of the present invention may be admixed with suitable carriers for application to interior and/or exterior areas for control of flea larvae.

The compositions of the present invention may be employed as animal feeds, animal feed premixes or feed concentrates. Feed concentrates and feed premixes, useful in the practice of the invention, may be prepared by admixing about 0.25% to 35% by weight of a subject anthelmintic compound, preferably a Structure 1-46 compound, with about 99.75% to 65% by weight of a suitable agronomic carrier or diluent. Carriers suitable for use include 0.75% to 35% by weight of a physiologically acceptable alcohol such as benzyl alcohol, phenethyl alcohol or propylene glycol, 0 to about 10% by weight of a vegetable oil such as corn oil or soybean oil, or propylene glycol and about 30% to 95% by weight of a sorptive, edible organic carrier such as corn grits, wheat middlings, soybean meal, expanded corn grits, extracted corn meal or the like or a sorptive silica or a silicate. These feed premixes or concentrates may be admixed with the appropriate amount of animal feed to provide the animals with about 0.5 ppm to 1,000 ppm and preferably about 1 ppm to 500 ppm of the compound in the animal's diet. These premixes or concentrates may also be used as top dressings for the animal's daily ration and applied across the top of the daily ration in sufficient amount to provide the animal with about 0.5 ppm to 1,000 ppm and preferably about 1 ppm to 500 ppm of the active ingredient, based on the animal's total feed.

The subject anthelmintic compounds, and particularly the Structure 1-46 compounds, most particularly Structure 22, 23, and Structure 48-290 compounds, may be administered to the animals in or with their drinking water.

The compound may also be administered in the form of a pill, tablet, bolus, implant, capsule, or drench, containing sufficient anthelmintic compound to provide the treated animal with about 0.01 mg/kg to 100 mg/kg of animal body weight per day of the compound. These dosage forms are prepared by intimately and uniformly mixing the active ingredient with suitable finely divided diluents, fillers, disintegrating agents and/or builders such as starch, lactose, talc, magnesium stearate, vegetable gums, or the like. These unit dosage formulations may be varied with respect to the total weight and content of anthelmintic compound depending upon the kind and size of the animal to be treated, the severity or type of infection encountered and the weight of the host.

Alternatively, the anthelmintic compound may be administered to animals parenterally, for example, by intraruminal, intramuscular, or subcutaneous injection in

which the active ingredient is dissolved or dispersed in a liquid carrier. For this type administration the compound may be dispersed in a physiologically acceptable solvent for subcutaneous injection, or it may be dispersed in a fat or wax or mixture thereof containing an oil, buffer, surfactant, stabilizer, preservative and salt. Components useful in these preparations include carbowax, aluminum monostearate gel, diethyl succinate, soya oil, glyceral dioleate, saline, and capric/caprylic triglycerides.

The subject anthelmintic compounds may also be applied topically to the larger animals such as swine, sheep, cattle, and horses and companion animals such as dogs and cats in the form of aqueous dips or sprays. For this type administration, the active compound is generally prepared as a wettable powder, emulsifiable concentrate, aqueous flowable, or the like, which is mixed with water at the site of treatment and applied topically to the hide, skin, or hair of the animal. Such sprays or dips usually contain about 0.5 ppm to 5,000 ppm and preferably about 1 ppm to 3,000 ppm of the compound.

Advantageously, the subject anthelmintic compounds may also be prepared as pour-on formulations and poured on the backs of the animals such as swine, cattle, sheep, horses, poultry, and companion animals to protect them against infestation by nematodes, acarids, and arthropod endo- and ectoparasites. Such pour-on compositions are generally prepared by dissolving, dispersing, or emulsifying the anthelmintic compound in a suitable nontoxic pharmacologically acceptable diluent for pour-on and administration. The diluent must be compatible with the compound and should not be a source of irritation or damage to the animals hide, skin, or hair. Such diluents include vegetable oils, spreading oils, polyhydric alcohols, aliphatic or aromatic hydrocarbons, esters of fatty acids, and lower alkyl ketones.

A typical pour-on formulation includes about 0.5% to 30% by weight of the anthelmintic compound, about 30% to 60% by weight of an aliphatic or aromatic hydrocarbon, mono or polyhydric alcohol, lower alkyl ketone or mixtures thereof, 0 to about 20% by weight of a vegetable or mineral oil and about 0.5% to 30% by weight of a spreading oil. Another typical pour-on contains about 45% by weight of xylene, about 15% by weight of the anthelmintic compound, about 10% by weight of corn oil or mineral oil, about 25% by weight of cyclohexanone and about 5% by weight of other pharmacologically acceptable spreading agents, antifoam agents, surfactants, or the like.

The subject anthelmintic compounds may also be prepared as ear tags for animals, particularly quadrupeds such as cattle and sheep. The tags may be prepared by stirring together about 55% to 60% by weight of a vinyl dispersion resin, having an inherent viscosity of about 1.20 and an average particle size of about 0.75 microns, a curing temperature range of about 120°C to 180°C, with about 28% by weight of butylbenzylphthalate. Stirring is continued, and about 1.5% by weight of ca/Zn stearate stabilizer is added along with about 7.0% of the compound and 2.8% of epoxidized soybean oil. The resulting mixture is deaerated for 15 to 20 minutes at 125 mm/Hg. This mixture can be coated on an ear tag blank by dipping and the resulting tag cured at about 145°C to 150°C for about five minutes.

The compounds of Formulae I-V, Structure 47, particularly Structures 1-46, and particularly Structures 22, 23, and 48-290 are nematicidal and can be used to control nematodes in crop plants. Therefore, in a further preferred aspect of the invention, there is provided a method for killing or controlling nematodes which comprises applying to the locus of the pests or to a plant susceptible to attack by the pest an effective amount of a compound having any of Structures 1-46, preferably Structure 47, and particularly Structures 22, 23, and 48-290, as defined herein.

The term "controlling" extends to non-lethal effects which result in the reduction or prevention of damage to the host plant or animal and the limitation of nematode population increase. These effects may be the result of chemical induced disorientation, immobilisation, or hatch prevention or induction. The chemical treatment may also have deleterious effects on nematode development, reproduction, or viability.

The compounds of the invention can be used against both plant-parasitic nematodes and nematodes living freely in the soil. Examples of plant-parasitic nematodes are: ectoparasites, for example Xiphinema spp., Longidorus spp., and Trichodorous spp.; semi-endoparasites, for example, Tylenchulus spp.; migratory endoparasites, for example, Pratylenchus spp., Radopholus spp., and Scutellonema spp.; sedentary endoparasites, for example, Heterodera spp., Globodera spp., and Meloidogyne spp.; and stem and leaf endoparasites, for example, Ditylenchus spp., Aphelenchoides spp., and Hirshmaniella spp..

The Formulae I-V compounds, Structure 47 compounds, and preferably the compounds of Structures 1-46, more preferably the compounds of Structures 22, 23, and 48-290, display nematicidal activity against different types of nematodes including the cyst nematode. The subject compounds may also be used to combat and control infestations of insect pests such as Lepidoptera, Diptera, Homoptera, and Coleoptera (including Diabrotica i.e. corn rootworms) and also other invertebrate pests, for example, acarine pests. The insect and acarine pests which may be combated and controlled by the use of the invention compounds include those pests associated with agriculture (which term includes the growing of crops for food and fiber products), horticulture and animal husbandry, forestry, the storage of products of vegetable origin, such as fruit, grain and timber, and also those pests associated with the transmission of diseases of man and animals. Examples of insect and acarine pest species which may be controlled by the subject compounds include:

Myzus persicae (aphid)
Aphis gossypii (aphid)
Aphis fabae (aphid)
Megoura viceae (aphid)
Aedes aegypti (mosquito)
Anopheles spp. (mosquitos)
Culex spp. (mosquitos)
Dysdercus fasciatus (capsid)
Musca domestica (housefly)
Pieris brassicae (white butterfly)
Plutella maculipennis (diamond back moth)
Phaedon cochleariae (mustard beetle)
Aonidiella spp. (scale insects)
Trialeuroides spp. (white flies)
Bemisia tabaci (white fly)
Blattella germanica (cockroach)
Periplaneta americana (cockroach)
Blatta orientalis (cockroach)
Spodoptera littoralis (cotton leafworm)
Hellothis virescens (tobacco budworm)
Chortiocetes terminifera (locust)
Diabrotica spp. (rootworms)
Agrotis spp. (cutworms)
Chilo partellus (maize stem borer)
Nilaparvata lugens (planthopper)
Nephotettix cincticeps (leafhopper)
Panonychus ulmi (European red mite)

Panonychus citri (citrus red mite)
Tetranychus urticae (two-spotted spider mite)
Tetranychus cinnabarinus (carmine spider mite)
Phyllcoptruta oleivora (citrus rust mite)
Polyphagotarsonemus latus (broad mite)
Brevipalpus spp. (mites)

In order to apply the compound to the locus of the nematode, insect, or acarid pest, or to a plant susceptible to attack by the nematode, insect, or acarid pest, the compound is usually formulated into a composition which includes in addition to at least one of the subject anthelmintic compounds suitable inert diluent or carrier materials, and/or surface active agents. Thus, in two further aspects of the invention there is provided a nematicidal, insecticidal, or acaricidal composition comprising an effective amount of a subject anthelmintic compound and preferably of any of Structures 1-46, preferably compounds of Structure 47, more preferably as exemplified by Structures 22, 23, and 48-290, as defined herein and an inert diluent or carrier material and optionally a surface active agent.

The amount of active ingredient generally applied for the control of nematode pests is from 0.01 to 10 kg per hectare, and preferably from 0.1 to 6 kg per hectare.

The compositions can be applied to the soil, plant or seed, to the locus of the pests, or to the habitat of the pests, in the form of dusting powders, wettable powders, granules (slow or fast release), emulsion or suspension concentrates, liquid solutions, emulsions, seed dressings, fogging/smoke formulations or controlled release compositions, such as microencapsulated granules or suspensions.

Dusting powders are formulated by mixing the active ingredient with one or more finely divided solid carriers and/or diluents, for example natural clays, kaolin, pyrophyllite, bentonire, alumina, montmorillonite, kieselguhr, chalk, diatomaceous earths, calcium phosphates, calcium and magnesium carbonates, sulphur, lime, flours, talc, and other organic and inorganic solid carriers.

Granules are formed either by absorbing the active ingredient in a porous granular material for example pumice, attapulgite clays, fullers earth, kieselguhr, diatomaceous earths, ground corn cobs, and the like, or on to hard core materials such as sands, silicates, mineral carbonates, sulphates, phosphates, or the like. Agents which are

commonly used to aid in impregnation, binding or coating the solid carriers include aliphatic and aromatic petroleum solvents, alcohols, polyvinyl acetates, polyvinyl alcohols, ethers, ketones, esters, dextrins, sugars, and vegetable oils with the active ingredient. Other additives may also be included, such as emulsifying agents, wetting agents, or dispersing agents.

Microencapsulated formulations (microcapsule suspensions CS) or other controlled release formulations may also be used, particularly for slow release over a period of time, and for seed treatment.

Alternatively the compositions may be in the form of liquid preparations to be used as dips, irrigation additives or sprays, which are generally aqueous dispersions or emulsions of the active ingredient in the presence of one or more known wetting agents, dispersing agents or emulsifying agents (surface active agents). The compositions which are to be used in the form of aqueous dispersions or emulsions are generally supplied in the form of an emulsifiable concentrate (EC) or a suspension concentrate (SC) containing a high proportion of the active ingredient or ingredients. An EC is a homogeneous liquid composition, usually containing the active ingredient dissolved in a substantially non-volatile organic solvent. An SC is a fine particle size dispersion of solid active ingredient in water. To apply the concentrates they are diluted in water and are usually applied by means of a spray to the area to be treated. For agricultural or horticultural purposes, an aqueous preparation containing between 0.0001% and 0.1% by weight of the active ingredient (approximately equivalent to from 5-2000 g/ha) is particularly useful.

Suitable liquid solvents for ECs include methyl ketone, methyl isobutyl ketone, cyclohexanone, xylenes, toluene, chlorobenzene, paraffins, kerosene, white oil, alcohols, (for example, butanol), methylnaphthalene, trimethylbenzene, trichloroethylene, N-methyl-2-pyrrolidone, and tetrahydrofurfuryl alcohol (THFA).

Wetting agents, dispersing agents, and emulsifying agents may be of the cationic, anionic, or non-ionic type. Suitable agents of the cationic type include, for example, quaternary ammonium compounds, for example cetyltrimethyl ammonium bromide. Suitable agents of the anionic type include, for example, soaps; salts of aliphatic monoesters of sulphuric acid, for example sodium lauryl sulphate; salts of sulphonated

aromatic compounds, for example sodium dodecylbenzenesulphonate; sodium, calcium or ammonium lignosulphonate; or butylnaphthalene sulphonate; and a mixture of the sodium salts of diisopropyl- and triisopropylnaphthalenesulphonates. Suitable agents of the non-ionic type include, for example, the condensation products of ethylene oxide with fatty alcohols such as oleyl alcohol or cetyl alcohol; or with alkyl phenols such as octyl phenol, nonyl phenol, and octyl cresol. Other non-ionic agents are the partial esters derived from long chain fatty acids and hexitol anhydrides, the condensation products of the said partial esters with ethylene oxide, and the lecithins.

These concentrates are often required to withstand storage for prolonged periods and after such storage, to be capable of dilution with water to form aqueous preparations which remain homogeneous for a sufficient time to enable them to be applied by conventional spray equipment. The concentrates may preferably contain 1-85% by weight of the active ingredient or ingredients. When diluted to form aqueous preparations such preparations may contain varying amounts of the active ingredient depending upon the purpose for which they are to be used.

The subject anthelmintic compounds may also be formulated as powders (dry seed treatment DS or water disperible powder WS) or liquids (flowable concentrate FS, liquid seed treatment LS), or microcapsule suspensions CS for use in seed treatments. The formulations can be applied to the seed by standard techniques and through conventional seed treaters. In use the compositions are applied to the nematodes, to the locus of the nematodes, to the habitat of the nematodes, or to growing plants liable to infestation by the nematodes, by any of the known means of applying pesticidal compositions, for example, by dusting, spraying, or incorporation of granules.

The compounds of the invention may be the sole active ingredient of the composition or they may be admixed with one or more additional active ingredients such as nematicides, agents which modify the behavior of nematodes (such as hatching factors), insecticides, synergists, herbicides, fungicides or plant growth regulators where appropriate.

Suitable additional active ingredients for inclusion in admixture with the compounds of the invention may be compounds which will broaden the spectrum of activity of the compounds of the invention or increase their persistence in the location of

the pest. They may synergise the activity of the compound of the invention or complement the activity for example by increasing the speed of effect or overcoming repellency. Additionally multi-component mixtures of this type may help to overcome or prevent the development of resistance to individual components.

The particular additional active ingredient included will depend upon the intended utility of the mixture and the type of complementary action required. Examples of suitable insecticides include the following:

a) Pyrethroids such as permethrin, esfenvalerate, deltamethrin, cyhalothrin in particular lambda-cyhalothrin, biphenthrin, fenpropathrin, cyfluthrin, tefluthrin, fish safe pyrethroids for example ethofenprox, natural pyrethrin, tetramethrin, s-bioallethrin, fenfluthrin, prallethrin, and 5-benzyl-3-furylmethyl-(E)-(1R,3S)-2,2-dimethyl-3-(2-oxothiolan-3-ylidenem ethyl) cyclopropane carboxylate;

b) Organophosphates such as profenofos, sulprofos, methyl parathion, azinphos-methyl, demeton-s-methyl, heptenophos, thiometon, fenamiphos, monocrotophos, profenophos, triazophos, methamidophos, dimethoate, phosphamidon, malathion, chloropyrifos, phosalone, terbufos, fensulphothion, fonofos, phorate, phoxim, pyrimiphos-methyl, pyrimiphos-ethyl, fenitrothion, or diazinon;

c) Carbamates (including aryl carbamates) such as pirimicarb, cloethocarb, carbofuran, furathiocarb, ethiofencarb, aldicarb, thiofurox, carbosulphan, bendiocarb, fenobucarb, propoxur, or oxamyl;

d) Benzoyl ureas such as triflumuron or chlorofluazuron;

e) Organic tin compounds such as cyhexatin, fenbutatin oxide, or azocyclotin;

f) Macrolides such as avermectins or milbemycins, for example such as abamectin, avermectin, and milbemycin;

g) Hormones and pheromones;

h) Organochlorine compounds such as benzene hexachloride, DDT, endosulphan, chlordane, or dieldrin;

i) Amidines, such as chlordimeform or amitraz;

j) Fumigant agents;

k) nitromethylenes such as imidacloprid.

In addition to the major chemical classes of insecticide listed above, other insecticides having particular targets may be employed in the mixture if appropriate for the intended utility of the mixture. For instance, selective insecticides for particular crops, for example stemborer specific insecticides for use in rice such as cartap or buprofezin, can be employed. Alternatively, insecticides specific for particular insect species/stages, for example, ovo-larvicides such as chlofentezine, flubenzimine, hexythiazox, and tetradifon; motilicides such as dicofol or propargite; acaricides such as bromopropylate or chlorobenzilate; or growth regulators such as hydramethylon, cyromazin, methoprene, chlorfluazuron, and diflubenzuron may also be included in the compositions.

Examples of suitable synergists for use in the compositions include piperonyl butoxide, sesamax, safroxan, and dodecyl imidazole.

Suitable herbicides, fungicides, and plant-growth regulators for inclusion in the compositions will depend upon the intended target and the effect required.

An example of a rice selective herbicides which can be included is propanil, an example of a plant growth regulator for use in cotton is "Pix", and examples of fungicides for use in rice include blasticides such as blasticidin-S. The ratio of the compound of the invention to the other active ingredient in the composition will depend upon a number of factors including type of target, effect required from the mixture, etc. However in general, the additional active ingredient of the composition will be applied at about the rate as it is usually employed, or at a slightly lower rate if synergism occurs.

The anthelmintic compounds according to the invention also show fungicidal activity and may be used to control one or more of a variety of plant pathogens. In a further aspect the invention therefore includes a method of combating fungi which comprises applying to a plant, to a seed of a plant, or to the locus of the plant or seed a fungicidally effective amount of a compound as herein defined or a composition containing the same. The invention further includes a fungicidal composition comprising a fungicidally effective amount of a compound as herein defined and a fungicidally acceptable carrier or diluent therefor.

Examples of plant pathogens which the compounds or fungicidal compositions of the invention may control, methods by which fungi may be combatted and the form of suitable compositions, including acceptable carriers and diluents; adjuvants such as

wetting, dispersing, emulsifying, and suspending agents; and other ingredients, such as fertilizers and other biologically active materials, are described, for instance, in International application No. WO 93/08180, the content of which is incorporated herein by reference.

All of the U.S. patents cited herein are hereby incorporated by reference.

Following are examples which illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted. For clarity the following abbreviations shall be used throughout the examples:

AC:	Acylator
ACD:	Available Chemicals Directory
ACN:	Acetonitrile
AcOH:	Acetic Acid
AM:	Amine
AUC:	Area under curve
BOC:	t-Butoxycarbonyl
Hyp-OH:	Hydroxyproline
DCM:	Dichloromethane
DIEA:	N,N-Diisopropylethylamine
DIC:	1,3 -Diisopropylcarbodiimide
DMAP:	Dimethylaminopyridine
DMF:	N,N-Dimethylformamide
DMSO:	Dimethylsulfoxide
ESI:	Electrospray ionization
ESMS:	ElectroSprayMassSpectrometry
Fmoc:	9-Fluorenylmethoxycarbonyl
HOBT:	1-Hydroxybenzotriazole
KOH:	Potassium hydroxide
LC/MS:	Liquid Chromatography/Mass Spectroscopy
MS:	Mass Spectroscopy

NMM:	N-Methylmorpholine
NMP:	N-Methylpyrrolidinone
Pyr:	Pyridine
S:	Scaffold
SLE:	Solid liquid-liquid extraction
THF:	Tetrahydrofuran
TFA:	Trifluoroacetic acid
TLC:	Thin layer chromatography
dH_2O	Distilled Water

Example 1 – Preparation of Anthelmintic Compounds 1-46

The anthelmintic compounds of the subject invention can readily be produced using procedures well known to those skilled in the art.

A variety of anthelmintic compounds useful according to the subject invention can be readily prepared by a person skilled in this art having the benefit of the subject disclosure.

Example 2 – Nematicidal Activity of Anthelmintic Compositions 1-31

Caenorhabditis elegans adults were grown on Nematode Growth Medium (NGM) until they produced eggs, then the adults were removed.

The eggs were allowed to hatch, and the L1 larvae collected. See *The Nematode Caenorhabditis elegans* (1988) Cold Spring Harbor Laboratory Press. Using a Matrix Programmable Pipette, the L1s were distributed into 96-well tissue culture plates, 20 L1 in 50μl NGM per well. Antibiotic/Antimyoticwas added to each well, and 1% by weight *E. coli* strain HB101. The subject anthelmintic compounds were stored at 5mM in 100% DMSO. 0.7μl of compounds 1-31 were added to the left-most column of wells to yield a final concentration of 70μM in 1.4% DMSO, with 1.4% DMSO only as the control. The compounds were then subjected to 5 more 3-fold dilutions from left to right to yield 6 column concentrations of 70μM, 23.3μM, 7.8μM, 2.6μM, 0.9μM, and 0.3μM. Plates were stored in air-tight Rubbermaid plastic boxes at 20°C. The nematodes had cleared all control wells by day 4, and nematode viability was scored by visual examination

under a 100x dissecting microscope on day 5. A visual viability scoring system was used as follows:

WORM VISUAL SCORING GUIDE

Lethality:

Dead	only stiff L1s (no movement)
Dead (L4)	worms are dead, but at a later larval stage
L1	majority of worms are L1 (based on size)
	worms move when plate is tapped
L2	majority of worms are L2 (based on size)
L3	majority of worms are L3 (based on size)
L4	majority of worms are L4 (based on size)

Partial Penetrance:

AD	majority of worms are adult
#AD	5 adult worms or less

Broodsize Reductions:

B!	sterile	(0 – 25 progeny)
B	low broodsize	(25 – 100 progeny)
~B	moderate broodsize	(100 – 250 progeny)
<	reduced broodsize	(250 – 500 progeny)
OK	no effect	(~ 1000+ progeny)

If several classes of worms exist in a well, then all classes are scored. If adults are present, then the brood score is also recorded. Thus, "L1/L2" would mean a mixture of L1's and L2's are present in the well. "L4/#AD/B" would mean that a mixture of L4's and adults are resent in the well. The "#AD" would mean that there are 6 or less adults, and the "B" would mean that there were 100 progeny or less.

The results are reported in Table 1. Column V1 has a compound concentration of 70μM with sequential 3-fold dilutions reported in columns V2, V3, V4, V5, and V6, respectively, such that the V6 concentration was 0.3μM.

Table I.

		Dose Response Tracking			5 Day Visual Score					
DR#	HTS Tracking Library #	Structure#	Source P	Well Address	V1	V2	V3	V4	V5	V6
1575	AKC 111	1	N2 #93	5081:D10	Dead	Dead	L2	Dead(L3/L	#AD/B	OK
1647	AKC 112	2	N2 #98	5090:A10	L2/L3	L2/L3	L2/L3	L3/L4	#AD/~B	OK
1466	AKC 113	3	N2 #85	5061:A10	Dead	Dead	Dead	Dead(L2/L	L2/Dead(A	L4/#AD/B
1469	AKC 107	4	N2 #86	5061:D10	Dead	Dead(L2/L3)	L2/L3	Dead(L4)	L4/Dead(A	L2/Dead(L
1477	AKC 114	5	N2 #86	5061:D11	Dead	L3/Dead(L4)	L3	L3/Dead(L	L2/L3	~B
1476	AKC 108	6	N2 #86	5061:C11	Dead	Dead	L1	L1	L1/L2	L2/L3
1473	AKC 115	7	N2 #86	5061:H10	Dead	Dead(L2/L3)	L2/Dead(L2)	Dead(L2)	Dead(L2/L	L2/L3
035	AKC 119	11	N2 #126	5393:B4	#AD/B	#AD/B	#AD/B	#AD/B	#AD/B	<
2059	AKC 110	12	N2 #128	5399:C4	L1	L1	L1	L1	L1	L1
2083	AKC 120	13	N2 #130	5419:C4	L1	L2/L3	L1	L1/L2	#AD/~B	OK
2032	AKC 121	14	N2 #126	5389:C4	L1	L1	L1/L2	#AD/~B	#AD/B	<
2029	AKC 2153	15	N2 #126	5379:C4	L1	L1	L1/L2	#AD/B	#AD/B	#AD/B
1962	AKC 122	16	N2 #121	5373:B8	Dead	L1	#AD/B	#AD/B	#AD/B	OK
1388	AKC 104	17	N2 #80	5022:C4	L1/L2	L1/L2	L1/L2	#AD/B	L1/L2	L1/L2
1372	AKC 123	18	N2 #79	5016:B8	L1	L1/L2	#AD/B	<	#AD/B	#AD/~B
1402	AKC 124	19	N2 #81	5033:D8	#AD/B!	#AD/B!	L2/L3	L4/#AD/B	L4/#AD/B	L4/#AD/B
1396	AKC 125	20	N2 #80	5031:G8	L2/Dead(L3)	L2/Dead(L4)	L2	L2	#AD/B	<
1393	AKC 105	21	N2 #80	5031:G2	L2/Dead(L3)	L2/Dead(L3)	L2/Dead(L3)	L2/Dead(L	L2/Dead(L	L2/Dead(/
1164	AKC 126	22	N2 #64	4724:I:10	L1/L2	L1/L2	L1/L2	#AD/~B	~B	#AD/B
1174	AKC 102	23	N2 #65	4727:I:8	L1/L2	L1/L2	L2/L3	L3	#AD/B	B
806	AKC 103	24	N2 #149	4470:D10	L1/L2	Dead(L3/L4)	Dead(L4)	B	L4/#AD/B	<
18	AKC 171	25	N2 #2	2606:A1	Dead	L2	Dead(L4)/#A	L2/L3	<	L2/L3
433	AKC 128	26	N2 #31	3313:A10	Dead	Dead	Dead	L1	#AD/~B	OK
506	AKC 129	27	N2 #37	3315:A10	Dead	Dead	L1/L2	L1/L2	OK	L1/L2
484	AKC 130	28	N2 #35	3314:D10	Dead	#AD/~B	#AD/B	#AD/~B	OK	#AD/B!
486	AKC 131	29	N2 #35	3314:F10	Dead	L1	#AD/~B	#AD/~B	#AD/~B	<
568	AKC 132	30	N2 #41	3323:G4	Dead(L2)	Dead	Dead	#AD/B	#AD/B	Dead
569	AKC 133	31	N2 #41	3323:H4	Dead	Dead	Dead	Dead	Dead	Dead
187	AKC 340	32	N2 #14	2665:B5	L1	L1	#AD/B!	#AD/B!	#AD/B	B
133	AKC 134	33	N2 #10	2640:A11	Dead	Dead	Dead	#AD/B	#AD/B	OK
149	AKC 135	34	N2 #11	2641:A8	Dead	L1	L1/L2	#AD/B	~B	#AD/B!
				CONTROL	OK	OK	OK	OK	OK	OK

Example 3 – Nematicidal Activity of Anthelmintic Compositions 32-46

The *C. elegans* nematode activity assay for anthelmintic compounds 32-46 was similar to that described in Example 2 above, except for the following noted differences. The compound concentrations were adjusted to 140 μM and subjected to 2-fold dilutions to yield 140μM, 70μM, 35μM, 17.5μM, 8.8μM, 4.4μM, 2.2μM, and 1.09μM. The visual evaluation of viability was conducted at Day 4, and the results are presented in Table 2.

Table 2.

Compound	μM Concentration							
	140	70	35	17.5	8.8	4.4	2.2	1.09
AKC-138	L1	L1	L1	L2	~B	OK	OK	OK
AKC-144	L3/L4	L4/AD/B	B	~B	OK	OK	OK	OK
AKC-141	L1	L1	L1	<	OK	OK	OK	OK
AKC-116	L1/L2	L2/L3	L3	B!	B	OK	OK	OK
AKC-117	L1/L2	L2/L3	L3	B!	B	<	OK	OK
AKC-118	L2	L2/L3	L3	L4/AD/B!	B	~B	OK	OK
Control	OK	OK	OK	OK	OK	OK	OK	OK

Example 4 - Activity Against Nematode (*C. elegans*) Eggs

Compositions of the subject invention are surprisingly found to be ovicidal. The following procedures are used to test for lethal effects against nematode eggs.

Materials

As referred to herein, "S Medium" refers to "S basal" supplemented with $CaCl_2$, $MgSO_4$, and a trace metals solution as follow:

S basal

NaCl	5.857 g
1M potassium phosphate (pH 6)	50.0 ml
Cholesterol (5mg/ml in EtOH)	1.0 ml
dH_2O	
	1 L

The above preparation is then autoclaved. S basal can be stored until needed.

Just prior to use, S Medium is made from S basal by adding, asceptically, the following components to 1L S basal (components should first be autoclaved separately):

1M potassium citrate (pH 6)	10 ml
Trace metals solution (see below)	10 ml
1M $CaCl_2$	3 ml
1M $MgSO_4$	3 ml

Trace Metals solution

Na_2EDTA	1.86 g	(to 5mM)
$Fe_2SO_4 \cdot 7H_2O$	0.69 g	(to 2.5mM)
$MnCl_2 \cdot 4H_2O$	0.20 g	(to 1mM)
$ZnSO_4 \cdot 7H_2O$	0.29 g	(to 1mM)
$CuSO_4 \cdot 5H_2O$	0.025 g	(to 0.1mM)
dH_2O		
		1 L

Procedure:

1. Make anthelmintic compound dilutions as indicated in Examples 2-3.
2. To 500 µl of each dilution, added 10 µl of eggs (estimated >200 eggs/10 µl).
3. Mixed well and allowed to incubate at room temperature for from 30 minutes to 3 hours.
4. Centrifuge at 2000 rpm for 5 minutes at room temperature.
5. Pipette off supernatant.
6. Re-suspend in 500 µl S Medium.

7. Centrifuge at 2000 rpm for 5 minutes at room temperature
8. Pipette off supernatant.
9. Re-suspend in 300 µl S Medium.
10. Transfer 300 µl into 24-well tissue culture bioassay tray.
11. Add 2 µl of stationary phase *E. coli* to each well.
12. Score after 3 days at room temperature in the dark.

Example 5 – Additional Observations of Activity Against Nematode (*C. elegans*) Eggs

Additional tests are conducted to confirm the ovicidal activity. The following procedures are used.

1. Make anthelmintic compound dilutions to 2X concentrations shown in Example 4.
2. Distribute 0.5 ml of each dilution into 1.5-ml Eppendorf tubes.
3. Add 0.5 ml of *C. elegans* egg preparation to 0.5 ml 2X dilution to yield final exposure concentration.
4. Mix well and allow to incubate at room temperature for from 30 minutes to 3 hours.
5. Centrifuge at 2000 rpm for 5 minutes at room temperature.
6. Pipette off supernatant and re-suspend in 1.5 ml S Medium.
7. Spin as above for 2 minutes.
8. Pipette off supernatant and re-suspend in 1.5 ml S Medium.
9. Repeat #7.
10. Pipette off supernatant and re-suspend in 1.0 ml S Medium.
11. Add 280 µl of S Medium to each well of 24-well tissue culture plate.
12. Add 20 µl of each treated (and control) sample in triplicate into the respective wells.
13. Score after 3 days at room temperature in the dark.

Example 6 – Preparation of Anthelmintic Compounds 47, as specifically exemplified by Compounds 48 -290

While the anthelmintic compounds of the subject invention can readily be produced using procedures well known to those skilled in the art, the following is a preferred method of producing anthelmintic Compounds 47, and exemplified Compounds 48-290, as shown in Figures 48-290. The general library scheme resulting in Compounds 47 is depicted in Figure 291. Scaffolds 1-6, depicted in Figures 292-297, are convenient intermediates for generating Compounds 47, and can be made from boc-hydroxyproline.

Scaffold Synthesis.

In a 2 L Morton three-neck flask equipped with mechanical stirrer, finely powdered 85% KOH (93.50 g, 1.666 mol, EM Biosciences) was dissolved in DMSO (400 mL, Aldrich, HPLC grade) under an atmosphere of nitrogen. After stirring at ambient temperature for 15 min, the apparatus was stirred and cooled with an ice-water bath for 10 min. After this 10 min period, Boc-Hyp-OH (48.59 g, 0.210 mol, Novabiochem) was added in one portion. DMSO (ca. 10 mL) was used to rinse residual Boc-Hyp-OH off the neck of the flask. After stirring for 5 min, the completely homogeneous solution was treated with one portion of 3-methoxybenzyl bromide (187 g, 0.928 mol) to initiate symthesis of Scaffold 6 (Figure 297). DMSO (10 mL) was used to rinse residual 3-methoxybenzyl bromide off the neck of the flask. Other precursors useful in scaffold synthesis are listed in Table 8, where the "Entry" column corresponds to the Scaffold number desired. Caution: Alkylating agents are lacrymators and highly corrosive. Solutions of DMSO can potentially be highly toxic. After stirring at 0 ^{0}C for 15 min, the reaction mixture was warmed up to ambient temperature for 4 h. The reaction was monitored by the following procedure: the reaction mixture (0.5 mL) was aliquoted to a 4 mL glass vial and diluted with water (1 mL). The aliquot was acidified with 1 M aqueous $KHSO_4$ (0.5 mL) to pH 2-3 (tested by pH paper). Diethyl ether (2 mL) was added to the acidic mixture. The sample in the organic phase was analyzed by TLC (9:1 CH_2Cl_2/MeOH) by UV light and Ninhydrin spray. After the reaction was judged complete after 4 h by TLC, the reaction mixture was poured into water (1.2 L) in a 2 L Erlenmeyer flask. The Morton flask was rinsed with an additional portion of water (400 mL), and the aqueous wash was transferred into the Erlenmeyer flask. After stirring at ambient temperature for 5 min, the suspension was washed with diethyl ether (2x 1.2 L).

The aqueous phase was acidified with 87% concentrated H_3PO_4 (150 mL) to pH 2-3 (tested by pH paper). This solution was then extracted diethyl ether (2x 1.2L). The combined ether layers were washed with water (2x 650 mL), and saturated aqueous NaCl (2x 700 mL). The organic layer was dried over anhydrous $MgSO_4$ (VWR) for 30 min, filtered, and concentrated in vacuo. The crude material was then triturated with hexane twice and concentrated in vacuo overnight.

The following procedure was used for scaffold 1, 2, and 6, Figures 292, 293, and 297, but was not used for scaffold 3, 4, and 5, Figure 294, 295, and 296. A solution of crude product in diethyl ether (1L) was treated with cyclohexylamine (18 mL, 0.210 mol). Upon precipitation, the mixture was cooled with an ice bath, stirred for 20 min, and filtered through a Buchner funnel under vacuum. The complex was washed with diethyl ether (2x 250 mL) and hexane (2x 250 mL), and air-dried overnight.

A solution of the complex in water (500 mL) and diethyl ether (350 mL) was stirred at ambient temperature until all solid material dissolved. The solution was then acidified with 87% concentrated H_3PO_4 (40 mL) to pH 2-3. In a 1 L separatory funnel, the organic layer was separated from the aqueous layer. The aqueous layer was extracted with diethyl ether (350 mL). The combined organic layers were washed with 0.5 M $KHSO_4$ (350 mL), water (250 mL) and saturated aqueous NaCl (2x 300 mL). The combined organic layers were dried over anhydrous $MgSO_4$ for 15 min, and filtered. Concentration in vacuo provided 72.0 g (98%) of scaffold 6 as a yellow oil.

Step A. Carboxylic Acid Coupling.

DIC (0.824 mL, 5.265 mmol) was added to a CH2Cl2 solution (6 mL) of carboxylic acid from Step A (5.265 mmol) and the solution was allowed to sit for 15 min with occasional swirling. The mixture was then added to the thiophenol resin (1.5 g, 1.755 mmol). The vial was rinsed with CH_2Cl_2 (5 mL), and this solution was added to the resin. DMAP (0.214 g, 1.755 mmol) was then added to the slurry, and the mixture was shaken for at least 18 hr. The resin was then washed using the following solvents; (CH_2Cl_2,THF) 4x; CH_2Cl_2 4x, MeOH 3x. The resin was then dried on high vacuum overnight (ca. 16 h). The resin loading was determined by mass analysis as a percentage of theoretical. The resin was also qualitatively analyzed by IR, and an FeCl3/pyr test.

Step B. Resin Plating.

The resin from Step A (ca. 100 mg per well using flat well Falcon Plates) was placed in the wells of a clamped polyfiltronics microtiter plate (2.7 μM, GF/D) following the T.O.P #APD-602 "Resin transfer with Falcon (Rev. Code: 20 Apr 1998 DGP)."

Step C. Deprotection.

Both Steps C and D must be done sequentially on the same day. Using a Moduline, the resins were washed with CH_2Cl_2 2x. After placing plates in Hydra clamps, a solution (1 mL/well) of TFA/ CH_2Cl_2/anisole (50:48:2) was added by a Robbins Hydra. The plate was covered with a teflon sheet and clamped. Wells should point upward. The plates are shaken on a reciprocal shaker for 1 h. After freezing the bottom of the plates in dry ice, the plates are unclamped and TFA allowed to drain. Using a Moduline, the resin was then washed using the following solvents, CH_2Cl_2 3x, 20% Et_3N/CH_2Cl_2 3x, MeOH 3x, CH_2Cl_2 3x. The plates are placed back into a Hydra clamp with a Teflon sheet on the bottom.

Step D. Acylation.

Both Steps C and D must be done sequentially on the same day. Four different classes of reagents are used to acylate the unreactive 4-aminoalkyl substituent: sulfonyl chlorides (see Table 9), acid chlorides (see Table 9), isocyanates and isothiocyanates. Each acylator is dissolved in 0.702 M DIEA in CH_2Cl_2 and diluted to 0.351 M with CH_2Cl_2. A solution of each acylator (1 mL/well) was added to the appropriate well. The plate was clamped, and shaken overnight (ca. 16 h) on a reciprocal shaker. Wells should point upward. Using a Moduline, the resins were washed using the following solvents, (CH_2Cl_2, then MeOH) repeat 4x, CH_2Cl_2 4x. The plate is placed back into a Hydra clamp with a Teflon sheet on the bottom.

Table 8

Alkyl bromides and iodides.

These precursors were used in the scaffold synthesis.

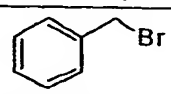
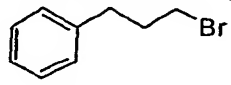
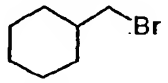
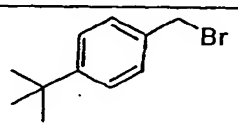
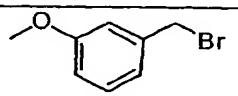
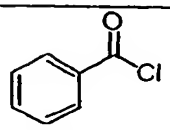
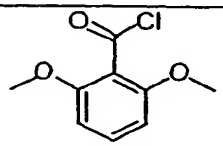
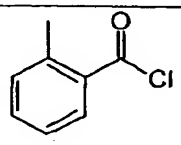
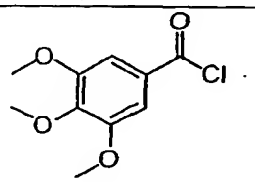
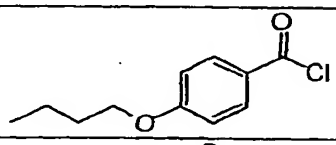
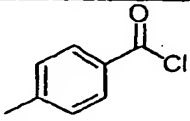
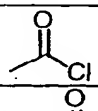
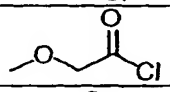
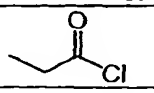
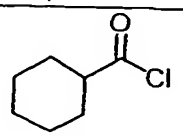
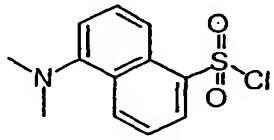
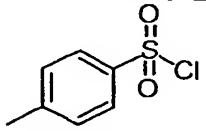
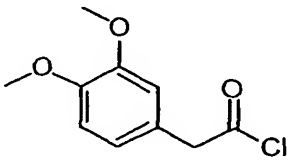
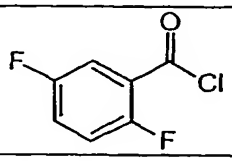
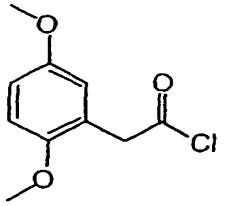
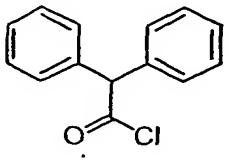
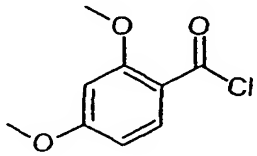
Entry	ACD	MW	Amount	Name	Structure
1	172	171.04	342 g	Benzyl bromide	
2	257	199.1	255 g	1-Bromo-3-phenylpropane	
3	1098	184.02	259 g	1-Iodobutane	
4	1509	177.09	345 g	(Bromomethyl) cyclohexane	
5	180	227.15	396 g	4-*tert*-Butylbenzyl bromide	
6	216590	201.07	301 g	3-Methoxy benzylbromide	

Table 9

Acid chlorides and sulfonyl chlorides.
The amount listed here is for one scaffold, which is a set of 12 plates, in the production library.

The final concentration is 0.351 M and the total volume is 50 mL.

Entry	ACD	MW	Amount(g)	Name	Structure
1	653	140.568 d=1.211	2.467	Benzoyl chloride	
2	665	200.62	3.521	2,6-Dimethoxybenzoyl chloride	
3	668	154.595 d=1.185	2.713	o-Toluoyl chloride	
4	675	230.646	4.048	3,4,5-Trimethoxybenzoyl chloride	
5	689	212.675 d=1.122	3.732	4-n-butoxybenzoyl chloride	
6	696	154.595 d=1.169	2.713	p-Toluoyl chloride	
7	719	78.4977 d=1.104	1.378	Acetyl chloride	
8	728	108.524 d=1.197	1.905	Methoxyacetyl chloride	
9	745	92.53 d=1.065	1.624	Propionyl chloride	
10	1456	146.616 d=1.096	2.573	Cyclohexanecarbonyl chloride	

Entry	ACD	MW	Amount(g)	Name	Structure
					
11	3985	269.751	4.734	Dansyl chloride	
12	7450	190.649	3.346	p-Toluenesulfonyl chloride	
13	9674	214.647	3.767	3,4-Dimethoxyphenylacetyl chloride	
14	9929	176.549 d=1.425	3.098	2,5-Difluorobenzoyl chloride	
15	12046	214.647	3.767	2,5-Dimethoxyphenylacetyl chloride	
16	13655	230.693	4.049	Diphenylacetyl chloride	
17	17527	200.62	3.521	2,4-Dimethoxybenzoyl chloride	

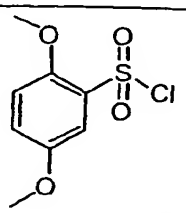
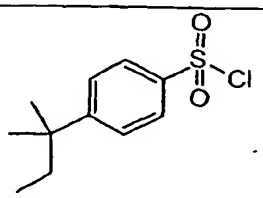
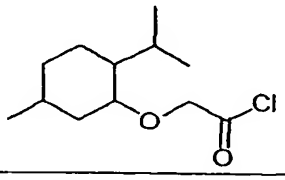
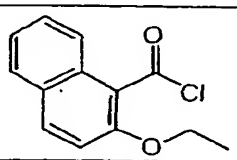
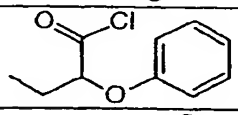
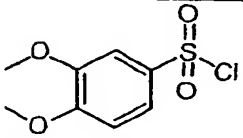
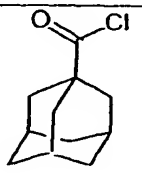
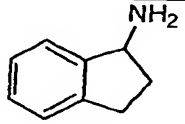
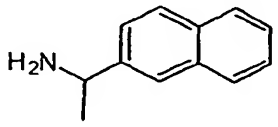
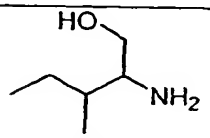
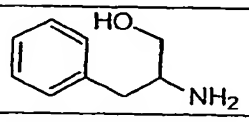
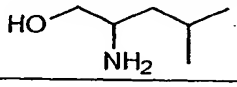
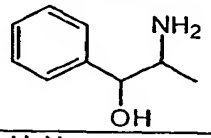
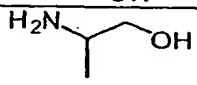
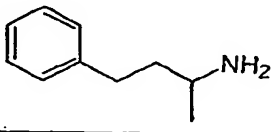
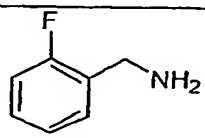
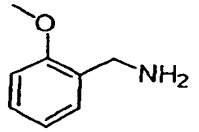
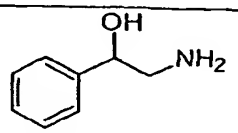
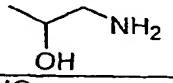
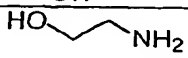
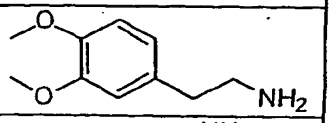
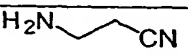
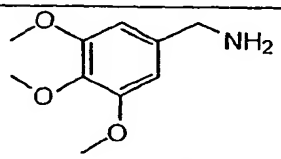
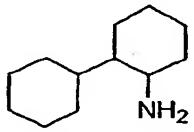
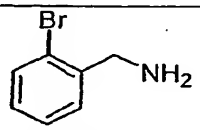
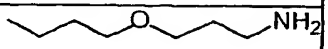
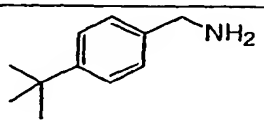
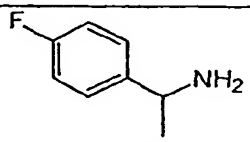
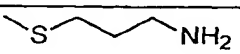
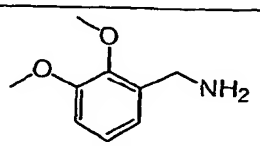
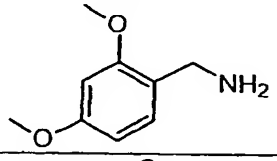
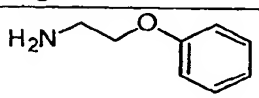
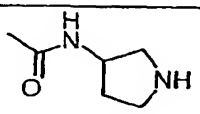
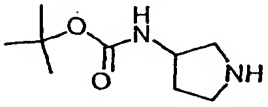
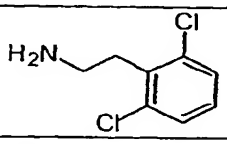
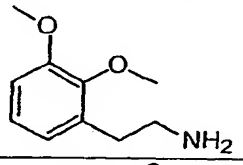
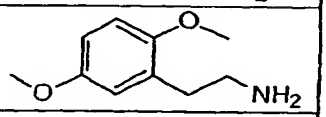
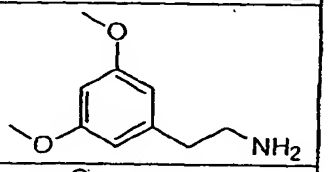
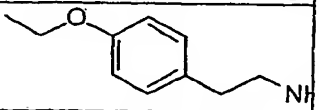
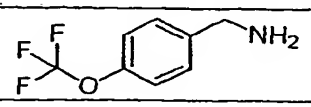
Entry	ACD	MW	Amount(g)	Name	Structure
18	24872	236.674	4.154	2,5-Dimethoxybenzenesulfonyl chloride	
19	41509	246.757	4.331	4-tert-Amylbenzenesulfonyl chloride	
20	44947	232.749 d=1.04	4.085	(-)-Menthoxyacetyl chloride	
21	46426	234.681	4.119	2-Ethoxy-1-naphthoyl chloride	
22	51569	198.648	3.486	2-Phenoxybutyryl chloride	
23	51769	236.674	4.154	3,4-Dimethoxybenzenesulfonyl chloride	
24	74724	198.691	3.487	1-Adamantanecarbonyl chloride	

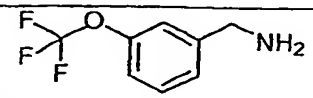
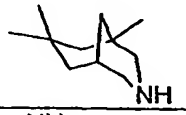
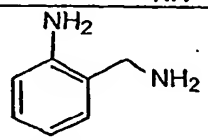
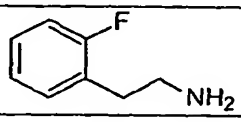
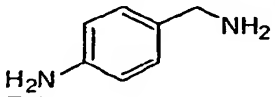
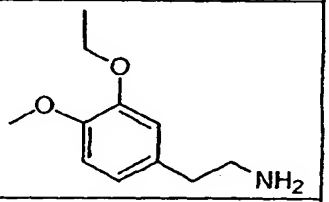
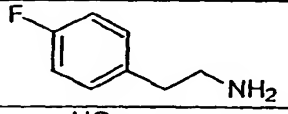
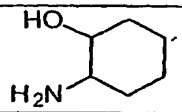
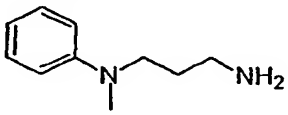
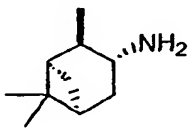
Table 10

Amine Diversity Elements.

Entry	ACD	MW	Amount (g)	Name	Structure
1	3799	133.19 d=1.038	1.172	1-Aminoindane	
2	4014	171.242 d=1.063	1.507	(+/-)-1-(1-Naphthyl)ethylamine	
3	4731	117.191 d=1.2	1.031	L-Isolecinol	
4	4732	151.208	1.331	L-Phenylalaninol	
5	4734	117.191 d=0.917	1.031	D-Leucinol	
6	8079	151.208	1.331	(1R,2S)-(-)-Norephedrine	
7	8085	75.1101 d=0.943	0.661	DL-2-Amino-1-propanol	
8	8090	149.236 d=0.922	1.313	1-Methyl-3-phenylpropylamine	
9	8107	125.15 d=1.095	1.101	2-Fluorobenzylamine	
10	8110	137.18 d=1.051	1.207	2-Methoxybenzylamine	

Entry	ACD	MW	Amount (g)	Name	Structure
11	8137	137.181	1.207	2-Amino-1-phenylethanol	
12	8139	75.1101 d=0.973	0.661	1-Amino-2-propanol	
13	8183	61.0833 d=1.012	0.538	Ethanolamine	
14	8188	181.234 d=1.074	1.595	3,4-Dimethoxyphenethyl amine	
15	11690	73.1379 d=0.740	0.644	n-Butylamine	
16	14820	70.0944 d=0.914	0.617	3-Aminopropionitrile	
17	17150	197.232 d=1.155	1.736	3,4,5-Trimethoxybenzyl amine	
18	21279	181.321 d=0.93	1.596	o-Aminobicyclohexyl	
19	25572	186.051 d=1.480	1.637	2-Bromobenzylamine	
20	25622	131.22 d=0.853	1.155	3-Butoxypropylamine	
21	40754	163.262 d=0.881	1.437	4-tert-Butylbenzylamine	
22	41323	139.172 d=1.059	1.225	4-Fluoro-α-methylbenzylamine	
23	41898	105.204 d=0.953	0.926	3-(Methylthio)propylamine	

Entry	ACD	MW	Amount (g)	Name	Structure
24	52392	167.207 d=1.130	1.471	2,3-Dimethoxybenzyl amine	
25	52393	167.207 d=1.113	1.471	2,4-Dimethoxybenzyl amine	
26	52975	137.181 d=1.048	1.207	2-Phenoxyethylamine	
27	59019	128.174	1.128	3-Acetamidopyrrolidine	
28	59040	186.253	1.639	3-(*tert*-butoxycarbonyl amino) pyrrolidine	
29	60612	190.072 d=1.28	1.673	2,6-Dichlorophenethyl amine	
30	60613	181.234 d=1.09	1.595	2,3-Dimethoxy phenethyl amine	
31	60614	181.234 d=1.09	595	2,5-Dimethoxy phenethyl amine	
32	60618	181.234 d=1.07	1.454	3,5-Dimethoxy phenethyl amine	
33	60620	165.234 d=0.99	1.682	4-Ethoxyphenethylamine	
34	61237	191.151 d=1.252	1.682	4-(Trifluoromethoxy) benzylamine	

Entry	ACD	MW	Amount (g)	Name	Structure
35	61267	191.151 u=1.252	1.349	3-(Trifluoromethoxy) benzylamine	
36	66934	153.267 d=0.902	1.075	1,3,3-Trimethyl-6-azabicyclo(3.2.1)octane	
37	75408	122.17	1.225	2-Aminobenzylamine	
38	75502	139.172 d=1.066		2-Fluorophenethylamine	
39	75513	122.17 d=1.078	1.075	4-Aminobenzylamine	
40	79755	195.26 d=1.05	1.718	3-Ethoxy-4-methoxy phenethylamine	
41	134208	139.172 d=1.076	1.225	4-Fluorophenethylamine	
42	191368	115.175	1.014	2-Aminocyclohexanol	
43	191602	164.25 d=1.00	1.445	*n*-(3-Aminopropyl)-*n*-methylaniline	
44	192238	153.267 d=0.909	1.349	(1R,2R,3R,5S)-(-)-Isopinocampheylamine	

Step E. Product Cleavage.

After washing with dioxane 2x, the resin from Step D was treated with the appropriate amine (0.8 mL of a 0.4 M solution in 1,4-dioxane, 0.32 mmol), selected from those listed in Table 10. The plates were shaken on a reciprocal shaker in a clamped plate at ambient temperature for 48 h. Wells should point upward. After the bottoms of the plates are frozen, polyfiltronics plate is placed on a Beckman square well plate and the crude products collected. The resins were washed with 1,4-dioxane (0.35 mL, 2x). After freezing the dioxane solutions in -80 °C freezer for 1 h, the products are lyophilized for at least 4 h.

Step F. SLE.

Removal of the excess amine starting material was accomplished by solid phase liquid-liquid extraction using Varian Chem Elut material packed into a polyfiltronics plate (10 micron PP/P). The Chem Elut (≈2.0 g) is treated with 2.0 N HCl (0.6 mL per well) followed by addition of the above product from Step E in 4:1 CH_2Cl_2/THF (1 mL). After allowing the product solution to elute for 15 min into the Beckman plate, the source plate was washed with 4:1 CH_2Cl_2/THF (0.350 mL), and each wash was transferred immediately to the SLE plate. Each 4:1 CH2Cl2/THF wash was allowed to drain for 15 min. The products were then concentrated in vacuo with Genevac following S.O.P. #APC-203-000 "Genevac Evaporator (Rev. Code: 23 July 1998 BW)" and analyzed by LC and MS.

Development.

Early Development: Several synthetic pathways were explored for the library synthesis of hydroxyproline derivatives. After amine addition to bromomethyl Wang resin, Fmoc-Hyp-OH was coupled to solid-supported amine with DIC (5 eq.) and HOBt (2.5 eq.) in NMP. PyBrop (2 eq.), and DIEA (4 eq.) in DCM also gave the desired product, as shown in Figure 298 . However, the Mitsunobu reaction in polyfiltronics plates failed. Heat generated from the high reaction concentration and poor mixing contributed to the failure of this reaction. In some cases, intramolecular cyclization or elimination occurred during the Mitsunobu reaction. Cleavage of linker was also observed.

As shown in Figure 299, an alternate route required coupling Fmoc-Hyp-OH on bromomethyl Wang resin, and introducing the final diversity element in solution as the last step.

Figure 300 depicts the result of using diamines on nitrophenol carbonate linker, which gave low yield of the desired product.

Solution phase syntheses of scaffolds functionalized with the first diversity element were then considered as a strategy for library generation. After introduction of the phenols on the hydroxyproline scaffold via Mitsunobu reaction, extensive chromatographic purification and low yields of these scaffolds made this route less desirable for library generation. Accordingly, the original protocol was modified to allow for alkylation on the alcohol moiety of the hydroxyproline, and a preferred library synthesis was the result. (Figure 301).

Scaffold Synthesis.

A practical synthesis of alkylated hydroxyproline scaffolds was developed. The alkylation was driven to completion using 400 mol% instead of 200 mol% excess alkylating reagent. The reaction was executed under an atmosphere of nitrogen because KOH is hydroscopic. DMSO also needs to be anhydrous. In the work up procedure, H_3PO_4 is the preferred acidifying agent since the use of $KHSO_4$ resulted in the precipitation of solids. Cyclohexylamine was also used to remove an unknown byproduct. No chromatography was involved in the syntheses.

Scaffold Coupling.

After scaffolds were coupled using DIC/DMAP, coupling was confirmed by $FeCl_3$/pyridine test. The test was performed by dissolving about 50 mg of resin in pyridine (0.5 mL) and adding a 0.5 M chloroform solution of $FeCl_3$ (0.5 mL). The resin was washed with CH_2Cl_2 and examined. Any color change to a dark color indicates free thiophenol. With free thiophenol resin, the beads will turn dark green-black. The test will indicate no free phenol if no color change from original resin color is observed. This is not a quantitative test, but a qualitative measure of resin loading.

Acylation.

Acid chlorides, sulfonyl chlorides, isocyanates, and isothiocyanates were generally soluble in DCM. Carboxylic acids were generally soluble in DMF.

Amine cleavage.

a. Although pyridine is reported to be a suitable solvent for cleavage, 1,4-dioxane also worked well.

b. Secondary amine cleavage requires much more time (36-48 h) than the primary amine cleavage (24 h).

SLE.

a. 4:1 CH_2Cl_2/THF used as elution solvent for SLE. In CH_2Cl_2, some products were insoluble.

b. Priming volume increased from 0.4 mL to 0.6 mL of 2 N HCl per well.

Plating.

After SLE, 4:1 ACN/MeOH used to dissolve products for QC samples.

Example 7 Nematicidal Activity of Anthelmintic Compositions 48-290

The nematicidal activity of anthelmintic Compositions 48-290 were determined in accordance with the procedure outlined in Example 2. The results are reported in Table 3.

			HTS Data											
HTS Tracking			Initial HTS Run			Follow-up HTS Run				5 Day Visual Score					
AKC #	MP #	Well	mOD	% Run	Visual Score	mOD	% Run	Visual Score	Well Addr	V1	V2	V3	V4	V5	V6
1259	4715	A7	169	83%	Dead	181	118%	4AD/B	4715:A7	L1	<	OK	OK	OK	OK
1260	4715	B7	187	92%	Dead	203	133%	L1/L2	4715:B7	L1	<	OK	OK	OK	OK
1261	4715	C7	196	96%	Dead	197	129%	L1/L2	4715:C7	L1	~B	OK	OK	OK	OK
1262	4715	D7	182	89%	Dead	191	125%	L1/L2	4715:D7	L1	~B	OK	OK	OK	OK
1263	4715	E7	200	98%	Dead	207	135%	1AD/B!	4715:E7	L1	#AD/~B	OK	OK	OK	OK
										L1	L1	L1/L2	OK	OK	OK
1264	4715	F7	206	101%	Dead	195	127%	1AD/B!	4715:F7	L1	#AD/B	OK	OK	OK	OK
1265	4715	G7	203	100%	Dead	188	123%	L1/L2	4715:G7	L1	#AD/~B	OK	OK	OK	OK
1266	4715	H7	197	97%	Dead	180	118%	2AD/B!	4715:H7	L1	<	OK	OK	OK	OK
1267	4715	E9	208	102%	L1/L2/L3	201	131%	B - AD Husks	4715:E9	L2/L3	~B	OK	OK	OK	OK
1268	4715	E10	198	97%	Dead	198	129%	4AD/B	4715:E10	L1	OK	OK	OK	OK	OK
1269	4715	F10	193	95%	Dead	202	132%	3AD/B	4715:F10	L1	<	OK	OK	OK	OK
1270	4715	G10	195	96%	Dead/1AD	192	125%	4AD/B	4715:G10	L1	OK	OK	OK	OK	OK
										B!	B!	OK	OK	OK	OK
1271	4715	H10	193	95%	1L3/1L4	171	112%	B	4715:H10	#AD/B!	OK	OK	OK	OK	OK
1272	4716	A7	166	81%	Dead	191	125%	Dead	4716:A7	L1/L2	<	OK	<	OK	OK
1273	4716	B7	189	93%	Dead	212	139%	L1/L2	4716:B7	L1	#AD/B	OK	OK	OK	OK
1274	4716	C7	183	90%	Dead	200	131%	3AD/B!	4716:C7	L1	<	OK	OK	OK	OK
1275	4716	D7	180	88%	Dead	195	127%	1AD/B!	4716:D7	L1	<	OK	OK	OK	OK
1276	4716	E7	184	90%	Dead	198	129%	L1/L2	4716:E7	L1	<	OK	OK	OK	OK
1277	4716	F7	197	97%	Dead	207	135%	1AD/B!	4716:F7	L1	<	OK	OK	OK	OK
										L1	L1	L1	OK	OK	OK
1278	4716	G7	201	99%	Dead	199	130%	L1/L2	4716:G7	L1	#AD/B	OK	OK	OK	OK
1279	4716	H7	201	99%	Dead	170	111%	B	4716:H7	L1	OK	OK	OK	OK	OK
1280	4716	F10	201	99%	Dead/1AD	182	119%	B	4716:F10	L1/L2	OK	OK	OK	OK	OK
1281	4717	A7	169	83%	Dead	190	124%	3AD/B!	4717:A7	L1	<	OK	<	OK	OK
1282	4717	B7	186	91%	Dead	220	144%	L1/L2	4717:B7	L1	~B	OK	OK	OK	OK
1283	4717	C7	195	96%	Dead	204	133%	3AD/B!	4717:C7	L1	~B	OK	OK	OK	OK
1284	4717	D7	182	89%	Dead	201	131%	1AD/B!	4717:D7	L1	#AD/B	OK	OK	OK	OK
										B!	B!	B!	OK	OK	OK
1285	4717	E7	197	97%	Dead	218	142%	2AD/B!	4717:E7	L1	~B	OK	OK	OK	OK
1286	4717	F7	192	94%	Dead	218	142%	L1/L2	4717:F7	L1	#AD/B	OK	OK	OK	OK
1287	4717	G7	206	101%	Dead	198	129%	2AD/B	4717:G7	L1	<	OK	OK	OK	OK
1288	4717	H7	212	104%	Dead	184	120%	5AD/B	4717:H7	L1	<	OK	OK	OK	OK
1289	4717	D10	192	94%	L1/1L4	191	125%	0AD/B! - AD Husks	4717:D10	L2/L3	L4/#AD/B!	~B	OK	OK	OK
1290	4717	E10	196	96%	Dead	195	127%	2L4/3AD/B	4717:E10	#AD/B	OK	OK	OK	OK	OK
1291	4717	H10	208	102%	L1/1L4	227	148%	B	4717:H10	L2/L3	OK	OK	OK	OK	OK
										L1	L1	L1	#AD/~B	OK	OK

1292	4718:E11	212	104%	L3/L4	180	118%	B	4718:E11	OK	#AD/B	OK	OK	OK	OK
1293	4720,D2	205	100%	AD/B! - No P, No Eggs, D	185	121%	B	4720:D2	L3/L4	L3/L4	<	OK	OK	OK
1294	4720 D3	209	102%	L1/L2	208	136%	Dead(L4/AD)	4720:D3	L3/L4	L3/L4	L3/L4	OK	OK	OK
1295	4720 D8	212	104%	L1/L2/Dead(L3/L4)	204	133%	Dead(L4/AD)	4720:D8	L3/L4	L3/L4	L3/L4	#AD/B!	OK	OK
1296	4720 D10	202	99%	Dead(L4)	212	139%	Dead(AD)	4720:D10	L3/L4	L3/L4	L3/L4	#AD/~B	OK	OK
1297	4721 E1	220	108%	L2	190	124%	B - AD Husks	4721:E1	L3/L4	#AD/B	#AD/B	OK	OK	OK
1298	4721 E8	218	107%	Dead/2L4	227	148%	L2/L3	4721:E8	L2/L3	L3/L4	<	OK	OK	OK
									B!	B!	B!	OK	OK	OK
1299	4721 E10	210	103%	5AD/B	206	135%	B - Dying AD	4721:E10	L1/L2	#AD/B	~B	OK	OK	OK
1300	4721 E11	209	102%	L2/L3/1AD/B!	192	125%	L4/AD/B	4721:E11	B	#AD/B	OK	OK	OK	OK
1301	4722 F1	216	106%	Dead	248	162%	L3/L4/Dead(L4)	4722:F1	L1	L1/L4	#AD/B!	#AD/B	OK	OK
1302	4723 D7	200	98%	L1/L2/L3	203	133%	B! - Dead (L4/AD)	4723:D7	Dead(L3)	L2/L3	#AD/B	<	OK	OK
1303	4724 E9	207	101%	L3/L4/2AD/B! - No P, 1 B	212	139%	Dead(L4/AD)	4724:E9	L1	L2/L3	#AD/B	OK	OK	OK
126	4724 E10	210	103%	L2/L3/L4	220	144%	L2/L3	4724:E10	L1/L2	L1/L2	L1/L2	#AD/~B	~B	#AD/~B
1304	4727 E4	224	110%	L1/L2	218	142%	B! - Dying	4727:E4	L1	#AD/B	OK	OK	OK	OK
									L1	L1	L1	OK	OK	OK
1305	4727 A7	169	83%	Dead	163	107%	B	4727:A7	L1	#AD/~B	OK	OK	OK	OK
1306	4727 B7	187	92%	Dead	195	127%	L4/AD/B	4727:B7	L1	~B	<	OK	OK	OK
1307	4727 C7	186	91%	Dead	207	135%	1AD/B!	4727:C7	L1	L1	<	OK	OK	OK
1308	4727 D7	182	89%	Dead	191	125%	5AD/B	4727:D7	L1	#AD/B	<	OK	OK	OK
1309	4727 E7	192	94%	Dead	202	132%	5AD/B	4727:E7	L1	#AD/B	<	OK	OK	OK
1310	4727 F7	200	98%	Dead	164	107%	B	4727:F7	L1	<	<	OK	OK	OK
1311	4727 G7	201	99%	Dead	169	110%	L4/AD/B	4727:G7	L1	#AD/~B	OK	OK	OK	OK
									B!	B!	B!	OK	OK	OK
1312	4727 H7	215	105%	Dead	157	103%	B	4727:H7	Dead	#AD/B	OK	OK	OK	OK
102	4727 E8	224	110%	L2/L3/1AD	211	138%	B - AD Dying	4727:E8	L1/L2	L1/L2	L2/L3	L3	#AD/B	B
1313	4727 E9	215	105%	L2/L3/1AD	204	133%	B - AD Dying	4727:E9	L1	L2/Dead(L	~B	OK	OK	OK
1314	4727 A10	176	86%	L1	177	116%	B	4727:A10	L1	<	OK	OK	OK	OK
1315	4727 B10	184	90%	L1	202	132%	L3/L4/AD/B!	4727:B10	L1	~B	OK	OK	OK	OK
1316	4727 C10	189	93%	L1	157	103%	B	4727:C10	L1	OK	OK	OK	OK	OK
1317	4727 D10	175	86%	L1	196	128%	2L4/3AD/B!	4727:D10	L1	OK	OK	OK	OK	OK
									L1	L1	L1	#AD/B!	OK	OK
1318	4727 E10	192	94%	L1	172	112%	B	4727:E10	L1	<	OK	OK	OK	OK
1319	4727 F10	190	93%	L1	206	135%	L1/L2	4727:F10	L1	#AD/B	OK	OK	OK	OK
1320	4727 G10	194	95%	L1	204	133%	2L4/1AD/B!	4727:G10	L1	OK	OK	OK	OK	OK
1321	4727 H10	189	93%	L1	205	134%	B	4727:H10	L1	OK	OK	OK	OK	OK
1322	4728 C10	191	94%	L1/L2	171	112%	B	4728:C10	L1/L2	OK	OK	OK	OK	OK
1323	4728 D10	184	90%	1AD/B!	190	124%	B	4728:D10	L1/L2	OK	OK	OK	OK	OK
1324	4729 D6	199	98%	L1	189	124%	2AD/B	4729:D6	L2/Dead(L3)	L4/#AD/B	<	OK	OK	OK
									B!	B!	B!	OK	OK	OK
1325	4729 E7	202	99%	Dead	191	125%	B	4729:E7	Dead	<	OK	OK	OK	OK

1326	4729	D10	186	91%	L1	185	121%	B	4729:D10	L1	OK	OK	OK	OK	OK
1327	4729	E10	192	94%	L1	161	105%	B	4729:E10	#AD/B	OK	OK	OK	OK	OK
1328	4739	D7	176	86%	Dead	179	117%	B	4739:D7	L1	<	OK	OK	OK	OK
1329	4739	E7	194	95%	Dead	208	136%	4AD/B	4739:E7	L1	<	OK	OK	OK	OK
1330	4739	E9	200	98%	Dead	156	102%	3AD/~B	4739:E9	L1	OK	OK	OK	OK	OK
1331	4739	E10	210	103%	L2/L3	207	135%	5AD/B - Husks	4739:E10	L1/L2	OK	#AD/~B	OK	OK	OK
										L1	L1	L1	~B	OK	OK
1332	4740	B7	192	94%	Dead	189	124%	4AD/B	4740:B7	L1	#AD/~B	OK	OK	OK	OK
1333	4740	C7	192	94%	Dead	160	105%	B	4740:C7	L1	<	OK	OK	OK	OK
1334	4740	D7	183	90%	Dead	173	113%	B	4740:D7	L1	<	<	OK	OK	OK
1335	4740	F7	210	103%	Dead	172	112%	B	4740:F7	L1	<	OK	OK	OK	OK
1336	4740	G7	219	107%	Dead	147	96%	B	4740:G7	#AD/B!	B	OK	OK	OK	OK
1337	4740	G10	208	102%	L1	202	132%	B	4740:G10	L1	OK	OK	OK	OK	OK
1338	4741	D6	194	95%	L1/L2	200	131%	L2/L3	4741:D6	L1	OK	OK	OK	OK	OK
										B!	B!	B!	OK	OK	OK
1339	4741	A7	165	81%	Dead	181	118%	4AD/B	4741:A7	L1	<	OK	OK	OK	OK
1340	4741	B7	188	92%	Dead	165	108%	B	4741:B7	#AD/B	OK	OK	OK	OK	OK
1341	4741	D7	193	95%	Dead	176	115%	B	4741:D7	L1	OK	OK	OK	OK	OK
1342	4741	E7	195	96%	Dead	209	137%	3AD/B!	4741:E7	L1	<	OK	OK	OK	OK
1343	4741	F7	216	106%	Dead	211	138%	1AD/B!	4741:F7	L1	<	OK	OK	OK	OK
1344	4741	H7	208	102%	Dead	176	115%	B	4741:H7	L1	OK	OK	OK	OK	OK
1345	4741	B10	192	94%	1AD/B!	159	104%	B	4741:B10	#AD/B!	OK	OK	OK	OK	OK
										L1	L1	L1	OK	OK	OK
1346	4741	D10	198	97%	L1/1L4	190	124%	B - Dying AD	4741:D10	OK	L3/L4	OK	OK	OK	OK
1347	4741	F10	205	100%	Dead	182	119%	B	4741:F10	#AD/B!	OK	OK	OK	OK	OK
1348	4741	G10	208	102%	Dead/1AD/B!	190	124%	B	4741:G10	#AD/B!	OK	OK	OK	OK	OK
1349	4742	E11	218	107%	L2/L3	221	144%	L1/L2	4742:E11	L2/Dead(L3)	L2/Dead(L	B	#AD/B	#AD/B!	OK
1350	4744	D2	196	96%	Dead	200	131%	L4/Dead(L4/AD)	4744:D2	Dead(L2/L3)	OK	OK	OK	OK	OK
1351	4744	D3	208	102%	L2/L3	192	125%	B - AD Dying	4744:D3	L2/Dead(L3)	Dead(L3/L	B	OK	OK	OK
1352	4744	D8	208	102%	Dead	210	137%	Dead(L3/L4)	4744:D8	Dead(L2/L3)	#AD/B	OK	OK	OK	OK
										B!	B!	B!	OK	OK	OK
1353	4744	D10	197	97%	L2	203	133%	Dead(L4/AD)	4744:D10	Dead(L2/L3)	Dead(L3)	OK	OK	OK	OK
1354	4745	E1	220	108%	L2/L3/L4	192	125%	4AD/B	4745:E1	L1/L2	#AD/~B	OK	OK	OK	OK
1355	4745	E10	210	103%	L2/L3/L4	186	122%	B	4745:E10	L2/L3	<	OK	OK	OK	OK
1356	4746	F1	200	98%	Dead	256	167%	4AD/B! - No P, AD	4746:F1	L1	~B	OK	OK	OK	OK
1357	4747	D1	203	100%	Dead/2AD - Both Bag	174	114%	4AD/~B	4747:D1	L3/Dead(AD	<	<	OK	OK	OK
1358	4747	D7	209	102%	Dead	216	141%	Dead(AD)	4747:D7	Dead(L2/L3)	<	OK	OK	OK	OK
1359	4747	D8	206	101%	1AD/B	164	107%	5AD/~B	4747:D8	L2/L3	OK	OK	OK	OK	OK
										L1	L1	L1	L4/#AD/E	OK	OK
1360	4751	A7	159	78%	Dead	174	138%	1AD/B!	4751:A7	OK	#AD/~B	OK	OK	OK	OK
1361	4751	B7	188	92%	1AD/B	190	151%	1AD/B!	4751:B7	L1	L1	OK	OK	OK	OK

1362	4751:C7	192	94%	Dead	199	158% L1/L2/1L4	4751:C7	L1	#AD/~B	OK	OK	OK	OK
1363	4751 D7	185	91%	Dead	194	154% L1/L2	4751:D7	L1	#AD/~B	OK	OK	OK	OK
1364	4751 E7	192	94%	Dead	200	159% L1/L2	4751:E7	L1	#AD/B!	OK	OK	OK	OK
1365	4751 F7	192	94%	Dead	209	166% 1AD/B!	4751:F7	L1	B	OK	OK	OK	OK
1366	4751 G7	198	97%	Dead	191	152% L1/L2	4751:G7	L1	<	OK	OK	OK	OK
								B!	B!	B!	OK	OK	OK
1367	4751 H7	202	99%	Dead	184	146% 3AD/B	4751:H7	L1	OK	OK	OK	OK	OK
1368	4751 B10	190	93%	Dead	175	139% 2AD/B	4751:B10	L4/#AD/B	OK	OK	OK	OK	OK
1369	4751 C10	188	92%	2AD/B	174	138% B	4751:C10	#AD/B!	OK	OK	OK	OK	OK
1370	4752 B7	182	89%	Dead	193	153% L1/L2	4752:B7	L1	#AD/B	~B	OK	OK	OK
1371	4752 C7	191	94%	Dead	198	157% L1/L2	4752:C7	L1	#AD/B	OK	OK	OK	OK
1372	4752 D7	187	92%	Dead	185	147% L2/L3	4752:D7	L1	~B	OK	OK	OK	OK
1373	4752 E7	197	97%	Dead	198	157% L1/L2	4752:E7	L1	OK	OK	OK	OK	OK
								L1	L1	L1	L1	#AD/~B	OK
1374	4752 F7	213	104%	Dead	202	160% L1/L2	4752:F7	L1	#AD/B	<	OK	OK	OK
1375	4752 G7	200	98%	Dead	200	159% 1AD/B!	4752:G7	L1	#AD/B	<	<	OK	OK
1376	4752 H7	199	98%	Dead	208	165% L1/L2	4752:H7	L1	B	B	OK	OK	OK
1377	4752 B10	197	97%	L2/L3	163	129% B	4752:B10	#AD/B	OK	OK	OK	OK	OK
1378	4752 C10	195	96%	L1/L2	172	137% 4AD/B	4752:C10	L1	OK	OK	OK	OK	OK
1379	4752 E10	195	96%	1AD/B!	167	133% B	4752:E10	L1/L2	OK	OK	OK	OK	OK
1380	4752 F10	205	100%	Dead	179	142% B	4752:F10	L1	OK	OK	OK	OK	OK
								B!	B!	B!	OK	OK	OK
1381	4752 H10	199	98%	2AD/B	209	166% L1/L2	4752:H10	L1	OK	OK	OK	OK	OK
1382	4753 A7	168	82%	Dead	182	144% 1AD/B!	4753:A7	L1	OK	OK	OK	OK	OK
1383	4753 B7	191	94%	Dead	191	152% 1AD/B!	4753:B7	L1	~B	OK	OK	OK	OK
1384	4753 C7	187	92%	Dead	194	154% 1AD/B!	4753:C7	#AD/B	OK	OK	OK	OK	OK
1385	4753 D7	196	96%	Dead	195	155% L1/L2	4753:D7	L1	#AD/B	OK	OK	OK	OK
1386	4753 E7	194	95%	Dead	197	156% L1/L2	4753:E7	L1	L4/#AD/B!	#AD/~B	OK	OK	OK
1387	4753 F7	182	89%	Dead	207	164% L1/L2	4753:F7	L1/L2	#AD/B	OK	OK	OK	OK
								L1	L1	L1	#AD/~B	OK	OK
1388	4753 G7	177	87%	Dead	218	173% L1/L2	4753:G7	L1	#AD/B	OK	OK	OK	OK
1389	4753 H7	189	93%	Dead	203	161% L1/L2	4753:H7	L1/L2	#AD/B	<	OK	OK	OK
1390	4753 B10	188	92%	L1/L2	193	153% 5AD/B!	4753:B10	L1	OK	OK	OK	OK	OK
1391	4753 D10	193	95%	Dead	177	140% 5AD/B	4753:D10	L4/#AD/B!	OK	OK	OK	OK	OK
1392	4753 E10	192	94%	Dead	202	160% L1/L2	4753:E10	L1/L2	OK	OK	OK	OK	OK
1393	4753 F10	203	100%	Dead	212	168% L1/L2	4753:F10	L1/L2	OK	OK	OK	OK	OK
1394	4753 H10	207	101%	L2/L3/L4	175	139% 5AD/B	4753:H10	L4/#AD/B!	OK	OK	OK	OK	OK
								B!	B!	B!	OK	OK	OK
1395	4756 D8	260	127%	Dead	200	159% Dead(L4/AD)	4756:D8	Dead(L4)	Dead(L4)	OK	OK	OK	OK
1396	4758 F1	197	97%	Dead	161	128% B! - No P, Healthy,	4758:F1	#AD/B!	OK	OK	OK	OK	OK
1397	4758 F2	224	110%	2AD/B!	157	125% B - Healthy, Unhat	4758:F2	L4/#AD/B	OK	OK	OK	OK	OK

1398	4763	A7	170	83%	Dead	193	153%	L1/L2	4763:A7	#AD/B	OK	OK	OK	OK	OK
1399	4763	B7	191	94%	Dead	205	163%	1AD/B!	4763:B7	L1	<	OK	OK	OK	OK
1400	4763	C7	192	94%	Dead	192	152%	1AD/B!	4763:C7	L1/L2	OK	OK	OK	OK	OK
1401	4763	D7	183	90%	Dead	187	148%	L1/L2	4763:D7	#AD/B!	<	OK	OK	OK	OK
										L1	L1	L1	#AD/~B	OK	OK
1402	4763	E7	189	93%	Dead	199	158%	L1/L2	4763:E7	L1	#AD/B	OK	OK	OK	OK
1403	4763	F7	190	93%	Dead	202	160%	L1/L2	4763:F7	#AD/B!	OK	OK	OK	OK	OK
1404	4763	G7	201	99%	Dead	193	153%	1AD/B!	4763:G7	L1	OK	OK	OK	OK	OK
1405	4763	H7	184	90%	Dead	203	161%	L1/L2	4763:H7	L1	<	OK	OK	OK	OK
1406	4763	A10	162	79%	Dead	172	137%	2AD/B!	4763:A10	L1	OK	OK	OK	OK	OK
1407	4763	B10	173	85%	Dead	190	151%	L1/L2	4763:B10	L1	<	OK	OK	OK	OK
1408	4763	C10	191	94%	Dead/2AD/B! - No P	195	155%	L1/L2	4763:C10	L1	OK	OK	OK	OK	OK
										B!	B!	B!	OK	OK	OK
1409	4763	D10	180	88%	Dead	190	151%	L1/L2	4763:D10	L1	OK	OK	OK	OK	OK
1410	4763	E10	183	90%	Dead	199	158%	L1/L2	4763:E10	L1	B	OK	OK	OK	OK
1411	4763	F10	193	95%	Dead	199	158%	L1/L2	4763:F10	L1	<	OK	OK	OK	<
1412	4763	G10	190	93%	Dead	193	153%	3AD/B!	4763:G10	#AD/B!	<	OK	OK	OK	OK
1413	4763	H10	206	101%	1AD/B!	200	159%	1AD/B!	4763:H10	L1/L2	OK	OK	OK	OK	OK
1414	4764	A7	216	106%	Dead	182	144%	1AD/B!	4764:A7	L1	<	OK	OK	OK	OK
1415	4764	B7	228	112%	Dead	194	154%	2AD/B	4764:B7	L4/#AD/B!	<	OK	OK	OK	OK
										L1	L1	L1	L1	OK	OK
1416	4764	C7	234	115%	Dead	195	155%	1AD/B	4764:C7	L4/#AD/B!	OK	OK	OK	OK	OK
1417	4764	D7	227	111%	Dead	187	148%	1AD/B!	4764:D7	#AD/B!	<	OK	OK	OK	OK
1418	4764	E7	240	118%	Dead	195	155%	2AD/B!	4764:E7	#AD/B!	<	OK	OK	OK	OK
1419	4764	F7	243	119%	1AD/B!	203	161%	L1/L2	4764:F7	L1	B	OK	OK	OK	OK
1420	4764	G7	236	116%	Dead	178	141%	L1/L2	4764:G7	L1/L2	<	OK	OK	OK	OK
1421	4764	H7	230	113%	Dead	203	161%	L1/L2	4764:H7	L1	OK	OK	OK	OK	OK
1422	4764	A10	200	98%	Dead	182	144%	L1/L2	4764:A10	L1	OK	OK	OK	OK	OK
										B!	B!	B!	OK	OK	OK
1423	4764	B10	196	96%	Dead	198	157%	1AD/B!	4764:B10	L1/L2	<	OK	OK	OK	OK
1424	4764	C10	190	93%	Dead	197	156%	L1/L2	4764:C10	L1/L2	<	<	OK	OK	OK
1425	4764	D10	196	96%	Dead	193	153%	L1/L2	4764:D10	L1/L2	OK	OK	OK	OK	OK
1426	4764	F10	213	104%	Dead	211	167%	L1/L2	4764:F10	L1	<	OK	OK	OK	OK
1427	4764	G10	214	105%	Dead	208	165%	L1/L2	4764:G10	L1/L2	OK	OK	OK	OK	OK
1428	4764	H10	229	112%	Dead	218	173%	L2/L3	4764:H10	L1/L2	<	OK	<	OK	OK
1429	4765	A7	175	86%	Dead	181	144%	1AD/B!	4765:A7	#AD/B!	OK	OK	OK	OK	OK
										L1	L1	L1	L1	OK	OK
1430	4765	B7	185	91%	Dead	197	156%	1AD/B!	4765:B7	L1	L4/#AD/B	OK	OK	OK	OK
1431	4765	C7	195	96%	Dead	198	157%	L1/L2	4765:C7	L1	#AD/B	OK	OK	OK	OK
1432	4765	D7	187	92%	Dead	192	152%	L1/L2	4765:D7	L1	<	OK	OK	OK	OK
1433	4765	E7	190	93%	Dead	201	160%	1AD/B!	4765:E7	L1	OK	OK	OK	OK	<

1434	4765 F7	190	93%	Dead	193	153%	2AD/B!	4765:F7	#AD/B!	OK	OK	OK	OK	OK
1435	4765 G7	192	94%	Dead	195	155%	L1/L2	4765:G7	L1	OK	OK	OK	OK	OK
1436	4765 H7	203	100%	Dead	199	158%	L1/L2	4765:H7	L1/L2	B	<	OK	OK	OK
									B!	B	B!	OK	OK	OK
1437	4765 A10	161	79%	Dead	176	140%	4AD/B!	4765:A10	L1	<	OK	OK	OK	OK
1438	4765 B10	165	81%	Dead	196	156%	1AD/B!	4765:B10	L1	<	OK	OK	OK	OK
1439	4765 C10	180	88%	Dead	197	156%	2L4/2AD/B!	4765:C10	L1/L2	OK	OK	OK	OK	OK
1440	4765 D10	193	95%	Dead	194	154%	L1/L2	4765:D10	L1	#AD/B!	OK	OK	OK	OK
1441	4765 E10	171	84%	Dead	200	159%	L1/L2	4765:E10	L1	~B	OK	OK	OK	OK
1442	4765 F10	192	94%	Dead	205	163%	1AD/B!	4765:F10	L1	OK	OK	OK	OK	OK
1443	4765 G10	187	92%	Dead	207	164%	L1/L2	4765:G10	L1	OK	OK	OK	OK	OK
									L1/L2	L1	L1	L1	OK	OK
1444	4765 H10	180	88%	Dead	209	166%	L1/L2	4765:H10	L1	OK	OK	OK	OK	OK
1445	4770 F1	203	100%	Dead	201	160%	B! - No P, Healthy,	4770:F1	L1/L2	~B	OK	OK	OK	OK
1446	4770 F8	222	109%	L1/L2	172	137%	B	4770:F8	L4/#AD/B!	OK	OK	OK	OK	OK
1447	4775 A7	176	86%	1AD/B!	176	140%	1AD/B!	4775:A7	L1	<	<	<	<	OK
1448	4775 C7	192	94%	Dead	196	156%	1AD/B!	4775:C7	L1	~B	<	OK	OK	OK
1449	4775 D7	184	90%	Dead	188	149%	1AD/B!	4775:D7	L1	~B	~B	OK	OK	OK
1450	4775 E7	196	96%	Dead	203	161%	L1/L2	4775:E7	L1	#AD/B	OK	OK	OK	OK
									B!	B!	B!	OK	OK	OK
1451	4775 F7	205	100%	Dead	208	165%	L1/L2	4775:F7	L1	OK	OK	OK	OK	OK
1452	4775 G7	200	98%	Dead	184	146%	2AD/B!	4775:G7	L1	<	OK	OK	OK	OK
1453	4775 H7	190	93%	Dead	185	147%	1AD/B	4775:H7	L1	OK	OK	OK	OK	OK
1454	4775 E9	205	100%	L1/L2	181	144%	L4/AD/B	4775:E9	#AD/B	OK	OK	OK	OK	OK
1455	4775 A10	150	74%	Dead	167	133%	L1/L2	4775:A10	L1/L2	OK	OK	OK	OK	OK
1456	4775 B10	173	85%	Dead	183	145%	L1/L2	4775:B10	L1	OK	OK	OK	OK	OK
1457	4775 C10	178	87%	1AD/B!	183	145%	L1/L2	4775:C10	L1	~B	OK	OK	OK	OK
									L1	L1	L1	L1	OK	OK
1458	4775 D10	172	84%	Dead	180	143%	L1/L2	4775:D10	L1	~B	OK	OK	OK	OK
1459	4775 E10	171	84%	Dead	190	151%	L1/L2	4775:E10	L1	B	~B	OK	OK	OK
1460	4775 F10	188	92%	Dead	196	156%	L1/L2	4775:F10	L1	OK	OK	OK	OK	OK
1461	4775 G10	201	99%	1AD/B	181	144%	5AD/B	4775:G10	L1	OK	OK	OK	OK	OK
1462	4776 A7	168	82%	Dead	151	120%	3AD/~B	4776:A7	L1	<	OK	OK	OK	OK
1463	4776 B7	187	92%	Dead	175	139%	4AD/B	4776:B7	L1	OK	OK	OK	OK	OK
1464	4776 C7	195	96%	L1	179	142%	3AD/B	4776:C7	L1	<	OK	OK	OK	OK
									B!	B!	B!	OK	OK	OK
1465	4776 D7	186	91%	Dead	182	144%	2AD/B	4776:D7	L1	~B	OK	OK	OK	OK
1466	4776 E7	190	93%	1AD/B	198	157%	1AD/B!	4776:E7	L1	B	OK	OK	OK	OK
1467	4776 F7	200	98%	L1	182	144%	4AD/B	4776:F7	#AD/B	OK	OK	OK	OK	OK
1468	4776 G7	202	99%	Dead	182	144%	1AD/B!	4776:G7	L1	<	OK	OK	OK	OK
1469	4776 A10	166	81%	Dead	171	136%	L1/L2	4776:A10	L1	<	OK	OK	OK	OK

1470	4776	B10	178	87%	Dead	191	152%	1AD/B!	4776:B10	OK	OK	OK	OK	OK	OK
1471	4776	C10	179	88%	Dead	192	152%	3AD/B!	4776:C10	L1/L2	OK	OK	OK	OK	OK
										L1	L1	L1	<	OK	OK
1472	4776	D10	180	88%	1AD/B!	190	151%	L1/L2	4776:D10	B	OK	OK	OK	OK	OK
1473	4776	F10	190	93%	1AD/B	194	154%	4AD/B!	4776:F10	L1	~B	OK	OK	OK	OK
1474	4776	G10	196	96%	L1/L2	200	159%	1AD/B!	4776:G10	L1/L2	OK	OK	OK	OK	OK
1475	4776	H10	193	95%	3AD/B	191	152%	5AD/B	4776:H10	L1/L2	OK	OK	OK	OK	OK
1476	4777	D3	200	98%	L2/L3	185	147%	Dead(AD)	4777:D3	Dead(L2/L3)	<	<	OK	OK	L1
1477	4777	D6	199	98%	L2/Dead(L3/L4)	172	137%	B - AD Dying	4777:D6	Dead(L2/L3)	#AD/B	OK	OK	OK	OK
1478	4777	A7	176	86%	1AD/B	175	139%	3AD/B	4777:A7	L1	OK	OK	<	OK	OK
										B!	B!	B!	OK	OK	OK
1479	4777	B7	196	96%	Dead	189	150%	3AD/B	4777:B7	B	OK	OK	OK	OK	OK
1480	4777	C7	196	96%	Dead	199	158%	2AD/B	4777:C7	#AD/B!	<	OK	OK	OK	OK
1481	4777	D7	192	94%	1AD/B	189	150%	1AD/B!	4777:D7	L1	OK	~B	OK	OK	OK
1482	4777	E7	195	96%	1AD/B	194	154%	L1/L2	4777:E7	L1	<	OK	OK	OK	OK
1483	4777	F7	203	100%	Dead	203	161%	1AD/B!	4777:F7	L1	OK	OK	OK	OK	OK
1484	4777	G7	203	100%	Dead	198	157%	1AD/B!	4777:G7	L1	OK	OK	OK	OK	OK
1485	4777	H7	207	101%	Dead	199	158%	2AD/B!	4777:H7	L1/L2	OK	OK	OK	OK	OK
										L1	L1	L1	#AD/B	B	OK
1486	4777	A10	168	82%	L1/L2	145	115%	B	4777:A10	L1/L2	OK	OK	OK	OK	OK
1487	4777	B10	174	85%	Dead	193	153%	L1/L2	4777:B10	L1	OK	OK	OK	OK	OK
1488	4777	C10	182	89%	Dead	190	151%	L1/L2	4777:C10	L1	<	OK	OK	OK	OK
1489	4777	D10	192	94%	Dead	193	153%	L1/L2	4777:D10	L1	~B	OK	OK	OK	OK
1490	4777	E10	186	91%	Dead	198	157%	L1/L2	4777:E10	L1	OK	<	OK	OK	OK
1491	4777	F10	199	98%	Dead	204	162%	L1/L2	4777:F10	L1	OK	OK	OK	OK	OK
1492	4777	G10	209	102%	L1/L2	219	174%	4AD/B!	4777:G10	L1	OK	OK	OK	OK	OK
										B!	B!	B!	OK	OK	OK
1493	4777	H10	196	96%	L1/L2	209	166%	1AD/B!	4777:H10	L1	<	OK	OK	OK	OK
1494	4778	E11	210	103%	L1/L2	212	168%	L2/L3	4778:E11	L2/L3	#AD/B	OK	OK	OK	OK
1495	4780	D2	200	98%	L2	183	145%	3AD/B - Husks	4780:D2	Dead	#AD/B	OK	OK	OK	OK
1496	4780	D3	202	99%	L1/L2	193	153%	Dead(AD)	4780:D3	L3/L4	L4/#AD/B	OK	OK	OK	OK
1497	4780	D8	213	104%	Dead(AD)	197	156%	L4/AD/B - Husks	4780:D8	#AD/B	#AD/B	OK	OK	OK	OK
1498	4781	F1	211	103%	L1/L2	214	170%	L1/L2/L3	4781:F1	Dead	B	OK	OK	OK	OK
1499	4782	D7	203	100%	AD/B! - Dying, Bags	177	140%	B - Dying, Husks	4782:D7	Dead(L4)	Dead(AD)	OK	OK	OK	OK

Example 8 – Sheep Test I Experimental Procedure

Sheep naturally infected with a variety of gastrointestinal nematodes are purchased from local sources and are transported to the test site. The animals are housed in a manner to preclude further infection by nematode larvae. The animals are evaluated for the presence of adequate nematode burdens by performing a standard fecal egg per gram (EPG) count. Eggs are differentiated into the following groups: trichostrongyle (strongyle), Strongyloides, Trichuris, or Nematodinis. Only sheep judged by the study parasitologist to have adequate nematode infections are used retained as test subjects.

The sheep are fed good quality hay (no concentrated rations) and water ad libitum. Following a five-day acclimation period, the sheep are randomly assigned by EPG count into treatment groups which include non-treated Negative control (placebo); Positive Control (commercially available ivermectin for sheep): and various anthelmintic compounds of the present invention (test compound) dissolved in DMSO. The first replicate of 10 animals is randomly assigned to groups 1-10; the second replicate of 10 animals is randomly assigned to groups 1-10; and the third replicate of 10 animals is randomly assigned to groups 1-10. Thus 10 groups of 3 animals each is created.

The randomization is performed on fecal samples collected 24-48 hours prior to scheduled treatment. The EPG counts are performed according to Zimmerman Research SOP # NMEPG.99.01

On treatment day, the animals are weighed and divided into groups with three animals per group as follows:

GROUP 1: Non-treated negative control (placebo) of 10 ml of DMSO.

GROUP 2: Positive Control treatment of 200 mcg/kg commercially available ivermectin for sheep.

GROUP 3: Compound @ dissolved in DMSO.

GROUP 4: Compound @ dissolved in DMSO.

GROUP 5: Compound @ dissolved in DMSO.

GROUP 6: Compound @ dissolved in DMSO.

GROUP 7: Compound @ dissolved in DMSO.

GROUP 8: Compound @ dissolved in DMSO.

GROUP 9: Compound @ dissolved in DMSO.

GROUP10: Compound @ dissolved in DMSO.

The placebo (DMSO), the commercially available drug, and the test anthelmintic compounds are administered in a 3ml volume by subcutaneous injection using a sterile syringe fitted with a proper needle. The animal is adequately immobilized for injection of the placebo, commercially available drug, or test anthelmintic compound.

Following treatment, the animals are observed at hourly intervals for the first 8 hours, then daily until necropsy. They will continue to be housed in a manner to prevent further nematode infections. Fecal samples are taken for EPG counts on the 5th day and 7th day after treatment.

Seven days following treatment the sheep are humanely slaughtered in accordance with the Guide for the Care and Use of Laboratory Animals (DHEW Publication No. 86-23). Necropsy procedures are according to Zimmerman Research SOP # NCRGIH.99.01, Necropsy for Helminth Recovery, specifically for gastrointestinal nematodes. Fecal samples are taken for EPG counts during the sample collection process on this day. All animals are necropsied, but only the animals from the experimental treatment groups that have a significant egg count reduction on day 5 or day 7 have intestinal material collected for nematode recovery and identification.

Nematodes are recovered, identified, and enumerated according to Zimmerman Research SOP # NEMRECOVID.99.01. All individuals performing nematode recoveries are blinded to treatment versus control animals. Preliminary estimates of total nematodes recovered from each gut sample are provided prior to identification and enumerations by the study parasitologist. At the discretion of the study parasitologist, seven days after the drug administration fecal egg counts are performed and all animals showing 90% or better trichostrongylid egg reduction will be slaughtered using humane methods recommended by the AVMA. The neck blood vessels are severed and after the animal is completely exsanguinated, the abdomen is opened. The abomasum, the small and large intestines are tied at the omasal and pyloric openings, the duodenum, the end of the small intestine and at the end of the large intestine. Each section is transferred in a separate bucket containing warm water and is slit open and thoroughly washed. The epithelium

is inspected before it is removed. The thus prepared washings are saved in gallon jars. An appropriate preservative is added. If preservative is not available, all the intestinal washing should kept in a refrigerator. These washings are passed through a 100-mesh sieve (pore size 149 pm), and the residue is examined for the presence of worms under a dissecting microscope. Lugol's solution may be used to stain the worms. All worms are picked up counted and identified as to the species. An effort should be made to recover any immature forms present. The efficacy should be calculated using the controlled anthelmintic test.

$$\text{Percentage efficacy} = \frac{\text{(Mean number of worms in controls minus Mean number of worms in treated animal)}}{\text{Mean number of worms in controls}} \times 100$$

Results are depicted in Tables 4 and 5.

Table 4

Akkadix	AKK 101	Sheep	Trial	17-Jan			
		Rumen	Injection				
	Sheep	Weight/lbs		Worm	Counts		
	Number	1/17/2000	Abomasum	Abomasum	Small Intestine	Small Intest.	
			Haemonchus	Ostertagia	Trichostrongylus	Nematodirus	
Group	81	84	420	60	0	140	
Negative	75	116	500	860	320	2300	
Control	56	87	0	0	80	0	
Mean Ct.			307	307	133	813	
Group	83	98	0	0	0	0	
Ivermectin	92	129	0	0	0	0	
200mcg/kg	53	82	0	0	0	0	
Mean Ct.			0	0	0	0	
		%Efficacy	**100**	**100**	**100**	**100**	
Group	58	74	0	80	380	1660	
AKC 102	71	51	20	2440	3720	180	
1.4mg/kg	60	107	0	0	480	280	
Mean Ct.			7	840	1527	707	
		%Efficacy	**98**				

Table 5

Akkadix	Trial -1	Sheep	AKK 101	Strongyles	Strongyles		Strongyles	
	Sheep	Weight/lbs	Total	17-Jan	22-Jan		24-Jan	
	Number	1/12/2000	EPG-pre	EPG-pre	EPG-5day	% Change	EPG-7day	%Change
Group 1	58	73	4690	4640	300		260	94.40
AKC 102	71	48	1670	1630	310		NS	80.98
1.4mg/kg	60	100	310	40	10		0	100.00
Total / Mean		221	2223.33	2103.33	206.67	90.17	86.67	**95.88**
Group 2	83	91	2310	2000	10		0	100.00
Ivermectin	92	113	570	570	0		0	100.00
.2mg/kg	53	77	90	70	0		0	100.00
Total / Mean		281	990.00	880.00	3.33	99.62	0.00	**100.00**
Group 3	81	74	2240	2240	780		770	65.63
Negative	75	109	370	300	260		1360	-353.33
Control	56	80	40	40	30		30	25.00
Total / Mean		263	883.33	860.00	356.67	58.53	720.00	**16.28**

Example 9 – Sheep Test II Experimental Procedure

Sheep naturally infected with a variety of gastrointestinal nematodes are purchased from local sources and are transported to the test site. The animals are housed in a manner to preclude further infection by nematode larvae. The animals are evaluated for the presence of adequate nematode burdens by performing a standard fecal egg per gram (EPG) count. Eggs are differentiated into the following groups: trichostrongyle (strongyle), Strongyloides, Trichuris, or Nematodiris. Only sheep judged by the study parasitologist to have adequate nematode infections are retained as test subjects.

The sheep are fed good quality hay (no concentrated rations) and water ad libitum. Following a five day acclimation period, the sheep are randomly assigned by EPG count into the following treatment groups: Groups 1-9, various anthelmintic compounds of the present invention (test compound) dissolved in DMSO: Group 10, Positive Control (commercially available ivermectin for sheep); Group 11, non-treated Negative control (DMSO only). The first replicate of 11 animals is randomly assigned to groups 1-11; the second replicate of 11 animals is randomly assigned to groups 1-11; and the third replicate of 11 animals is randomly assigned to groups 1-11. Thus 11 groups of 3 animals each are created.

The randomization is performed on fecal samples collected 24-48 hours prior to scheduled treatment. The EPG counts are performed according to Zimmerman Research SOP # NMEPG.99.01.

GROUP 1: AKKADIX compound dissolved in DMSO.
GROUP 2: AKKADIX compound dissolved in DMSO.
GROUP 3: AKKADIX compound dissolved in DMSO.
GROUP 4: AKKADIX compound dissolved in DMSO.
GROUP 5: AKKADIX compound dissolved in DMSO.
GROUP 6: AKKADIX compound dissolved in DMSO.
GROUP 7: AKKADIX compound dissolved in DMSO.
GROUP 8: AKKADIX compound dissolved in DMSO.
GROUP 9: AKKADIX compound dissolved in DMSO.
GROUP 10: Positive Control treatment of 200 mcg/kg commercially available

ivermectin for sheep.

GROUP11: Non-treated negative control (placebo) of 3 ml of DMSO.

On treatment day, the animals are weighed, tagged, and divided into groups of three animals per group as follows:

The placebo (DMSO), the commercially available drug, and the test anthelmintic compounds are administered in a 3ml volume of DMSO by subcutaneous injection using a sterile syringe fitted with a sterile needle. The site of injection is clipped and swabbed with alcohol prior to injection. The animal is adequately immobilized for injection of the placebo, commercially available drug, or experimental compound.

Following treatment, the animals are observed at hourly intervals for the first 8 hours, then daily until necropsy. They are housed in a manner to prevent further nematode infections.

On the fifth day following treatment, fecal samples are obtained from each animal, properly labeled and used for EPG counts.

Seven days following treatment, all the sheep are weighed and humanely slaughtered in accordance with the Guide for the Care and Use of Laboratory Animals (DHEW Publication No. 86-23). Necropsy procedures are according to Zimmerman Research SOP # NCRGIH.00.01, Necropsy for Helminth Recovery, specifically for gastrointestinal nematodes. Fecal samples are taken for EPG counts during the sample collection process on this day.

Nematodes are recovered, identified, and enumerated according to Zimmerman Research SOP # NEMRECOVID.00.01. All individuals performing nematode recoveries are blinded to treatment versus control animals.

Anthelmintic efficacy is calculated using the controlled test procedure:

$$\% \text{ Efficacy} = \frac{\text{Mean number of worms in controls minus mean number of worms in treated}}{\text{Mean number of worms in controls}} \times 100$$

Results are depicted in Tables 6 and 7.

Table 6

Akkadix	AKK-102	Sheep	24-May				
	Sheep	Weight/lbs		Worm	Counts		
	Number	5/17/2000	Abomasum	Abomasum	Small Intestine	Small Intest.	Large Intest.
			Haemonchus	Ostertagia	Trichostrongylus	Nematodirus	Trichuris
Group	530	47	60	580	40	8500	5
Negative	1341	57	60	20	20	2520	15
Control	524	54	20	80	0	0	10
Mean Ct.			47	227	20	3673	10
Group	1347	45	0	0	0	100	0
Ivermectin	1336	58	20	0	0	100	0
200mcg/kg	539	47	0	0	0	0	0
Mean Ct.			7	0	0	67	0
		%Efficacy	**86**	**100**	**100**	**98**	
Group	1348	45	20	340			
AKC 102	1332	42	160	1380			
1mg/kg	1338	33	0	100			
Mean Ct.			60	607			
		%Efficacy	**-29**				

Table 7

Akkadix	Trial -2	Sheep	**AKK 102**	Strongyles	Strongyles		Strongyles	
	Sheep	Weight/lbs	Total	15-May	22-May		24-May	
	Number	5/17/2000	EPG-pre	EPG-pre	EPG-5day	% Change	EPG-7day	%Change
Group	1348	45	760	110	120		420	-281.82
AKC 102	1332	42	350	270	2332		570	-111.11
1mg/kg	1338	33	100	70	30		70	0.00
Total / Mean		120	403.33	150.00	827.33	-451.56	353.33	**-135.56**
Group	530	47	710	640	690		300	53.13
Negative	1341	57	160	120	160		340	-183.33
Control	524	54	70	60	140		50	16.67
Total / Mean		158	313.33	273.33	330.00	-20.73	230.00	**15.85**
Group 10	1334	41	560	530	690		290	45.28
AKC 110	536	40	280	220	850		1510	-586.36
3.5mg/kg	1339	46	70	40	0		30	25.00
Total / Mean		127	303.33	263.33	513.33	-94.94	610.00	**-131.65**
Group	1347	45	560	450	0		0	100.00
Ivermectin	1336	58	220	170	0		0	100.00
200mcg/kg	539	47	100	40	0		0	100.00
Total / Mean		150	293.33	220.00	0.00	100.00	0.00	**100.00**

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

Claims

What is claimed is:

1. A method for controlling nematodes which comprises contacting said nematodes with a nematode-controlling effective amount of a composition comprising at least one compound having Structure 47.

2. A method for controlling nematodes which comprises contacting said nematodes with a nematode-controlling effective amount of a composition comprising at least one compound having a structure selected from the group consisting of Structures 48-290.

3. The method of claim 2, wherein said compound is Compound 48.

4. The method of claim 2, wherein said compound is Compound 49.

5. The method of claim 2, wherein said compound is Compound 50.

6. The method of claim 2, wherein said compound is Compound 51.

7. The method of claim 2, wherein said compound is Compound 52.

8. The method of claim 2, wherein said compound is Compound 53.

9. The method of claim 2, wherein said compound is Compound 54.

10. The method of claim 2, wherein said compound is Compound 55.

11. The method of claim 2, wherein said compound is Compound 56.

12. The method of claim 2, wherein said compound is Compound 57.

1 13. The method of claim 2, wherein said compound is Compound 58.

1 14. The method of claim 2, wherein said compound is Compound 59.

1 15. The method of claim 2, wherein said compound is Compound 60.

1 16. The method of claim 2, wherein said compound is Compound 61.

1 17. The method of claim 2, wherein said compound is Compound 62.

1 18. The method of claim 2, wherein said compound is Compound 63.

1 19. The method of claim 2, wherein said compound is Compound 64.

1 20. The method of claim 2, wherein said compound is Compound 65.

1 21. The method of claim 2, wherein said compound is Compound 66.

1 22. The method of claim 2, wherein said compound is Compound 67.

1 23. The method of claim 2, wherein said compound is Compound 68.

1 24. The method of claim 2, wherein said compound is Compound 69.

1 25. The method of claim 2, wherein said compound is Compound 70.

1 26. The method of claim 2, wherein said compound is Compound 71.

1 27. The method of claim 2, wherein said compound is Compound 72.

1 28. The method of claim 2, wherein said compound is Compound 73.

1 29. The method of claim 2, wherein said compound is Compound 74.

1 30. The method of claim 2, wherein said compound is Compound 75.

1 31. The method of claim 2, wherein said compound is Compound 76.

1 32. The method of claim 2, wherein said compound is Compound 77.

1 33. The method of claim 2, wherein said compound is Compound 78.

1 34. The method of claim 2, wherein said compound is Compound 79.

1 35. The method of claim 2, wherein said compound is Compound 80.

1 36. The method of claim 2, wherein said compound is Compound 81.

1 37. The method of claim 2, wherein said compound is Compound 82.

1 38. The method of claim 2, wherein said compound is Compound 83.

1 39. The method of claim 2, wherein said compound is Compound 84.

1 40. The method of claim 2, wherein said compound is Compound 85.

1 41. The method of claim 2, wherein said compound is Compound 86.

1 42. The method of claim 2, wherein said compound is Compound 87.

1 43. The method of claim 2, wherein said compound is Compound 88.

1 44. The method of claim 2, wherein said compound is Compound 89.

1 45. The method of claim 2, wherein said compound is Compound 90.

1 46. The method of claim 2, wherein said compound is Compound 91.

1 47. The method of claim 2, wherein said compound is Compound 92.

1 48. The method of claim 2, wherein said compound is Compound 93.

1 49. The method of claim 2, wherein said compound is Compound 94.

1 50. The method of claim 2, wherein said compound is Compound 95.

1 51. The method of claim 2, wherein said compound is Compound 96.

1 52. The method of claim 2, wherein said compound is Compound 97.

1 53. The method of claim 2, wherein said compound is Compound 98.

1 54. The method of claim 2, wherein said compound is Compound 99.

1 55. The method of claim 2, wherein said compound is Compound 100.

1 56. The method of claim 2, wherein said compound is Compound 101.

1 57. The method of claim 2, wherein said compound is Compound 102.

1 58. The method of claim 2, wherein said compound is Compound 103.

1 59. The method of claim 2, wherein said compound is Compound 104.

1 60. The method of claim 2, wherein said compound is Compound 105.

1 61. The method of claim 2, wherein said compound is Compound 106.

1 62. The method of claim 2, wherein said compound is Compound 107.

1 63. The method of claim 2, wherein said compound is Compound 108.

1 64. The method of claim 2, wherein said compound is Compound 109.

1 65. The method of claim 2, wherein said compound is Compound 110.

1 66. The method of claim 2, wherein said compound is Compound 111.

1 67. The method of claim 2, wherein said compound is Compound 112.

1 68. The method of claim 2, wherein said compound is Compound 113.

1 69. The method of claim 2, wherein said compound is Compound 114.

1 70. The method of claim 2, wherein said compound is Compound 115.

1 71. The method of claim 2, wherein said compound is Compound 116.

1 72. The method of claim 2, wherein said compound is Compound 117.

1 73. The method of claim 2, wherein said compound is Compound 118.

1 74. The method of claim 2, wherein said compound is Compound 119.

1 75. The method of claim 2, wherein said compound is Compound 120.

1 76. The method of claim 2, wherein said compound is Compound 121.

1 77. The method of claim 2, wherein said compound is Compound 122.

1 78. The method of claim 2, wherein said compound is Compound 123.

1 79. The method of claim 2, wherein said compound is Compound 124.

1 80. The method of claim 2, wherein said compound is Compound 125.

1 81. The method of claim 2, wherein said compound is Compound 126.

1 82. The method of claim 2, wherein said compound is Compound 127.

1 83. The method of claim 2, wherein said compound is Compound 128.

1 84. The method of claim 2, wherein said compound is Compound 129.

1 85. The method of claim 2, wherein said compound is Compound 130.

1 86. The method of claim 2, wherein said compound is Compound 131.

1 87. The method of claim 2, wherein said compound is Compound 132.

1 88. The method of claim 2, wherein said compound is Compound 133.

1 89. The method of claim 2, wherein said compound is Compound 134.

1 90. The method of claim 2, wherein said compound is Compound 135.

1 91. The method of claim 2, wherein said compound is Compound 136.

1 92. The method of claim 2, wherein said compound is Compound 137.

1 93. The method of claim 2, wherein said compound is Compound 138.

1 94. The method of claim 2, wherein said compound is Compound 139.

1 95. The method of claim 2, wherein said compound is Compound 140.

1 96. The method of claim 2, wherein said compound is Compound 141.

1 97. The method of claim 2, wherein said compound is Compound 142.

1 98. The method of claim 2, wherein said compound is Compound 143.

1 99. The method of claim 2, wherein said compound is Compound 144.

1 100. The method of claim 2, wherein said compound is Compound 145.

1 101. The method of claim 2, wherein said compound is Compound 146.

1 102. The method of claim 2, wherein said compound is Compound 147.

1 103. The method of claim 2, wherein said compound is Compound 148.

1 104. The method of claim 2, wherein said compound is Compound 149.

1 105. The method of claim 2, wherein said compound is Compound 150.

1 106. The method of claim 2, wherein said compound is Compound 151.

1 107. The method of claim 2, wherein said compound is Compound 152.

1 108. The method of claim 2, wherein said compound is Compound 153.

1 109. The method of claim 2, wherein said compound is Compound 154.

1 110. The method of claim 2, wherein said compound is Compound 155.

1 111. The method of claim 2, wherein said compound is Compound 156.

1 112. The method of claim 2, wherein said compound is Compound 157.

1 113. The method of claim 2, wherein said compound is Compound 158.

1 114. The method of claim 2, wherein said compound is Compound 159.

1 115. The method of claim 2, wherein said compound is Compound 160.

1 116. The method of claim 2, wherein said compound is Compound 161.

1 117. The method of claim 2, wherein said compound is Compound 162.

1 118. The method of claim 2, wherein said compound is Compound 163.

1 119. The method of claim 2, wherein said compound is Compound 164.

1 120. The method of claim 2, wherein said compound is Compound 165.

1 121. The method of claim 2, wherein said compound is Compound 166.

1 122. The method of claim 2, wherein said compound is Compound 167.

1 123. The method of claim 2, wherein said compound is Compound 168.

1 124. The method of claim 2, wherein said compound is Compound 169.

1 125. The method of claim 2, wherein said compound is Compound 170.

1 126. The method of claim 2, wherein said compound is Compound 171.

1 127. The method of claim 2, wherein said compound is Compound 172.

1 128. The method of claim 2, wherein said compound is Compound 173.

1 129. The method of claim 2, wherein said compound is Compound 174.

1 130. The method of claim 2, wherein said compound is Compound 175.

1 131. The method of claim 2, wherein said compound is Compound 176.

1 132. The method of claim 2, wherein said compound is Compound 177.

1 133. The method of claim 2, wherein said compound is Compound 178.

1 134. The method of claim 2, wherein said compound is Compound 179.

1 135. The method of claim 2, wherein said compound is Compound 180.

1 136. The method of claim 2, wherein said compound is Compound 181.

1 137. The method of claim 2, wherein said compound is Compound 182.

1 138. The method of claim 2, wherein said compound is Compound 183.

1 139. The method of claim 2, wherein said compound is Compound 184.

1 140. The method of claim 2, wherein said compound is Compound 185.

1 141. The method of claim 2, wherein said compound is Compound 186.

1 142. The method of claim 2, wherein said compound is Compound 187.

1 143. The method of claim 2, wherein said compound is Compound 188.

1 144. The method of claim 2, wherein said compound is Compound 189.

1 145. The method of claim 2, wherein said compound is Compound 190.

1 146. The method of claim 2, wherein said compound is Compound 191.

1 147. The method of claim 2, wherein said compound is Compound 192.

1 148. The method of claim 2, wherein said compound is Compound 193.

1 149. The method of claim 2, wherein said compound is Compound 194.

1 150. The method of claim 2, wherein said compound is Compound 195.

1 151. The method of claim 2, wherein said compound is Compound 196.

1 152. The method of claim 2, wherein said compound is Compound 197.

1 153. The method of claim 2, wherein said compound is Compound 198.

1 154. The method of claim 2, wherein said compound is Compound 199.

1 155. The method of claim 2, wherein said compound is Compound 200.

1 156. The method of claim 2, wherein said compound is Compound 201.

1 157. The method of claim 2, wherein said compound is Compound 202.

1 158. The method of claim 2, wherein said compound is Compound 203.

1 159. The method of claim 2, wherein said compound is Compound 204.

1 160. The method of claim 2, wherein said compound is Compound 205.

1 161. The method of claim 2, wherein said compound is Compound 206.

1 162. The method of claim 2, wherein said compound is Compound 207.

1 163. The method of claim 2, wherein said compound is Compound 208.

1 164. The method of claim 2, wherein said compound is Compound 209.

1 165. The method of claim 2, wherein said compound is Compound 210.

1 166. The method of claim 2, wherein said compound is Compound 211.

1 167. The method of claim 2, wherein said compound is Compound 212.

1 168. The method of claim 2, wherein said compound is Compound 213.

1 169. The method of claim 2, wherein said compound is Compound 214.

1 170. The method of claim 2, wherein said compound is Compound 215.

1 171. The method of claim 2, wherein said compound is Compound 216.

1 172. The method of claim 2, wherein said compound is Compound 217.

1 173. The method of claim 2, wherein said compound is Compound 218.

1 174. The method of claim 2, wherein said compound is Compound 219.

1 175. The method of claim 2, wherein said compound is Compound 220.

1 176. The method of claim 2, wherein said compound is Compound 221.

1 177. The method of claim 2, wherein said compound is Compound 222.

1 178. The method of claim 2, wherein said compound is Compound 223.

1 179. The method of claim 2, wherein said compound is Compound 224.

1 180. The method of claim 2, wherein said compound is Compound 225.

1 181. The method of claim 2, wherein said compound is Compound 226.

1 182. The method of claim 2, wherein said compound is Compound 227.

1 183. The method of claim 2, wherein said compound is Compound 228.

1 184. The method of claim 2, wherein said compound is Compound 229.

1 185. The method of claim 2, wherein said compound is Compound 230.

1 186. The method of claim 2, wherein said compound is Compound 231.

1 187. The method of claim 2, wherein said compound is Compound 232.

1 188. The method of claim 2, wherein said compound is Compound 233.

1 189. The method of claim 2, wherein said compound is Compound 234.

1 190. The method of claim 2, wherein said compound is Compound 235.

1 191. The method of claim 2, wherein said compound is Compound 236.

1 192. The method of claim 2, wherein said compound is Compound 237.

1 193. The method of claim 2, wherein said compound is Compound 238.

1 194. The method of claim 2, wherein said compound is Compound 239.

1 195. The method of claim 2, wherein said compound is Compound 240.

1 196. The method of claim 2, wherein said compound is Compound 241.

1 197. The method of claim 2, wherein said compound is Compound 242.

1 198. The method of claim 2, wherein said compound is Compound 243.

1 199. The method of claim 2, wherein said compound is Compound 244.

1 200. The method of claim 2, wherein said compound is Compound 245.

1 201. The method of claim 2, wherein said compound is Compound 246.

1 202. The method of claim 2, wherein said compound is Compound 247.

1 203. The method of claim 2, wherein said compound is Compound 248.

1 204. The method of claim 2, wherein said compound is Compound 249.

1 205. The method of claim 2, wherein said compound is Compound 250.

1 206. The method of claim 2, wherein said compound is Compound 251.

1 207. The method of claim 2, wherein said compound is Compound 252.

1 208. The method of claim 2, wherein said compound is Compound 253.

1 209. The method of claim 2, wherein said compound is Compound 254.

1 210. The method of claim 2, wherein said compound is Compound 255.

1 211. The method of claim 2, wherein said compound is Compound 256.

1 212. The method of claim 2, wherein said compound is Compound 257.

1 213. The method of claim 2, wherein said compound is Compound 258.

1 214. The method of claim 2, wherein said compound is Compound 259.

1 215. The method of claim 2, wherein said compound is Compound 260.

1 216. The method of claim 2, wherein said compound is Compound 261.

1 217. The method of claim 2, wherein said compound is Compound 262.

1 218. The method of claim 2, wherein said compound is Compound 263.

1 219. The method of claim 2, wherein said compound is Compound 264.

1 220. The method of claim 2, wherein said compound is Compound 265.

1 221. The method of claim 2, wherein said compound is Compound 266.

1 222. The method of claim 2, wherein said compound is Compound 267.

1 223. The method of claim 2, wherein said compound is Compound 268.

1 224. The method of claim 2, wherein said compound is Compound 269.

1 225. The method of claim 2, wherein said compound is Compound 270.

1 226. The method of claim 2, wherein said compound is Compound 271.

1 227. The method of claim 2, wherein said compound is Compound 272.

1 228. The method of claim 2, wherein said compound is Compound 273.

1 229. The method of claim 2, wherein said compound is Compound 274.

2 230. The method of claim 2, wherein said compound is Compound 275.

1 231. The method of claim 2, wherein said compound is Compound 276.

1 232. The method of claim 2, wherein said compound is Compound 277.

1 233. The method of claim 2, wherein said compound is Compound 278.

1 234. The method of claim 2, wherein said compound is Compound 279.

1 235. The method of claim 2, wherein said compound is Compound 280.

1 236. The method of claim 2, wherein said compound is Compound 281.

1 237. The method of claim 2, wherein said compound is Compound 282.

1 238. The method of claim 2, wherein said compound is Compound 283.

1 239. The method of claim 2, wherein said compound is Compound 284.

1 240. The method of claim 2, wherein said compound is Compound 285.

1 241. The method of claim 2, wherein said compound is Compound 286.

1 242. The method of claim 2, wherein said compound is Compound 287.

1 243. The method of claim 2, wherein said compound is Compound 288.

1 244. The method of claim 2, wherein said compound is Compound 289.

1 245. The method of claim 2, wherein said compound is Compound 290.

FIG. 1

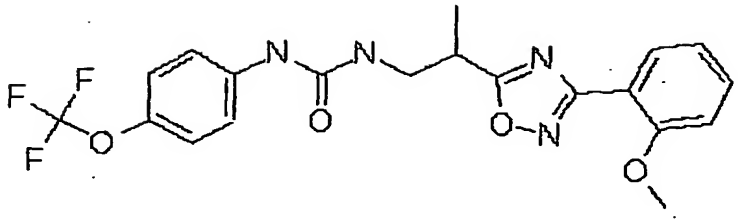


FIG. 2

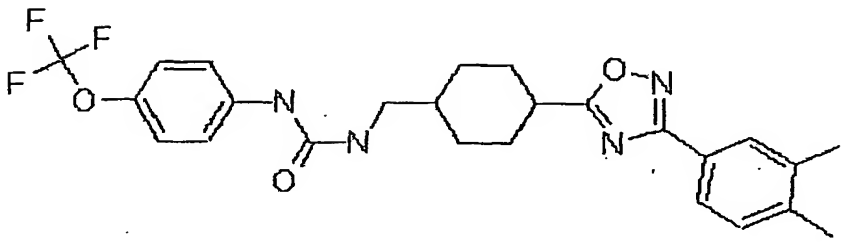


FIG. 3

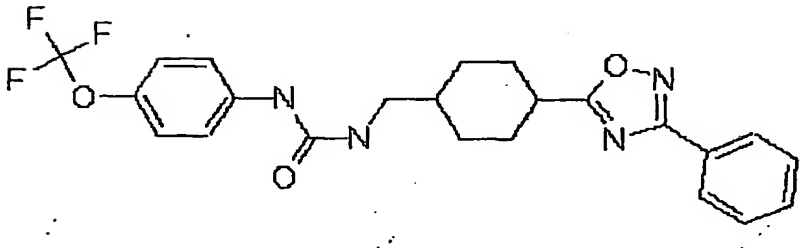


FIG. 4

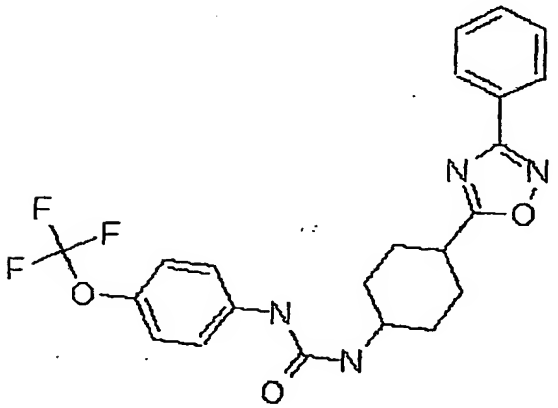


FIG. 5

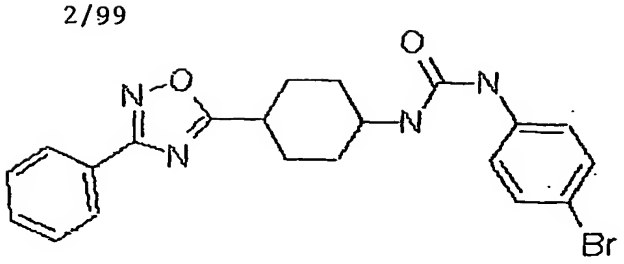


FIG. 6

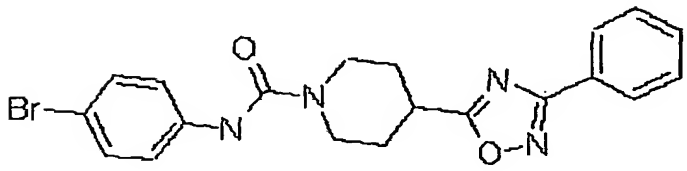


FIG. 7

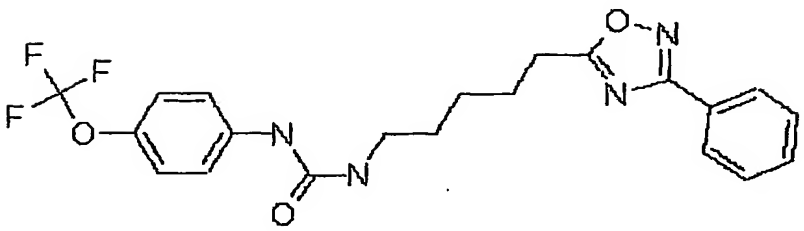


FIG. 8

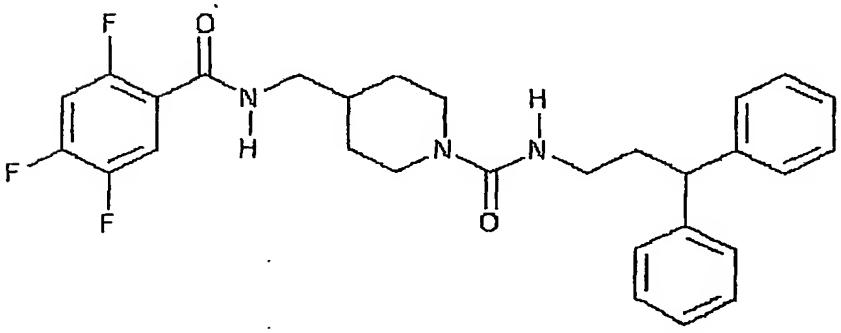


FIG. 9

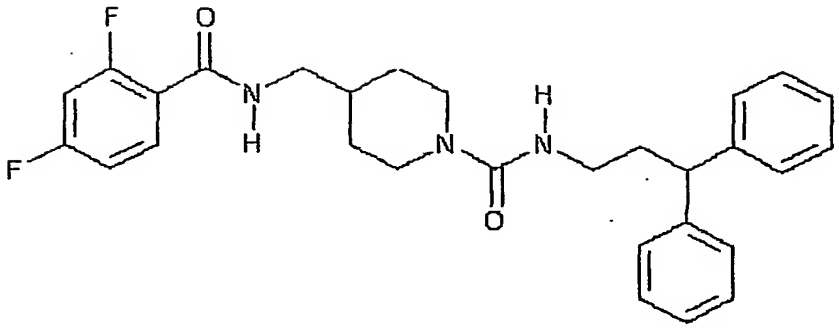


FIG. 10

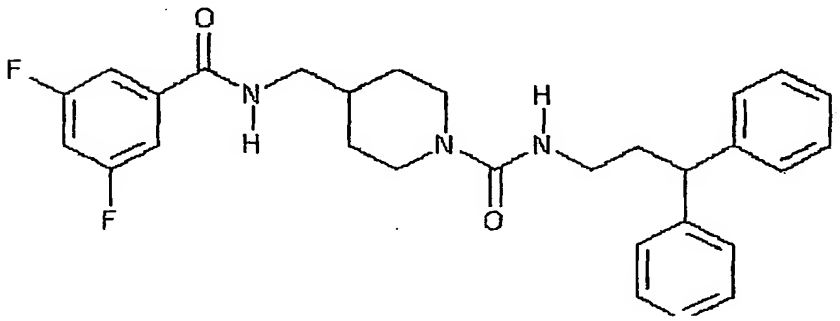


FIG. 11

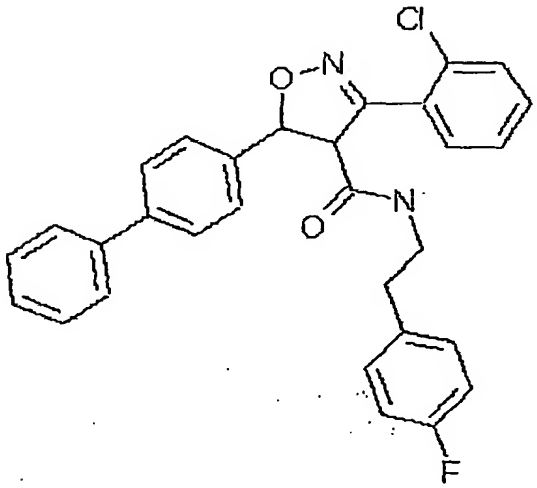


FIG. 12

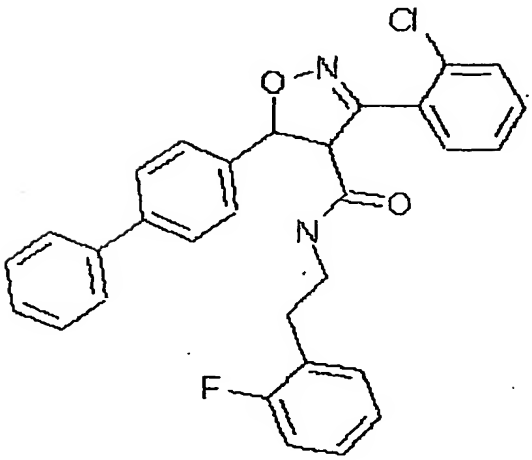


FIG. 13

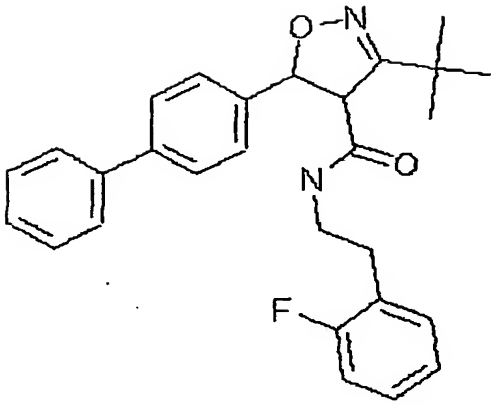


FIG. 14

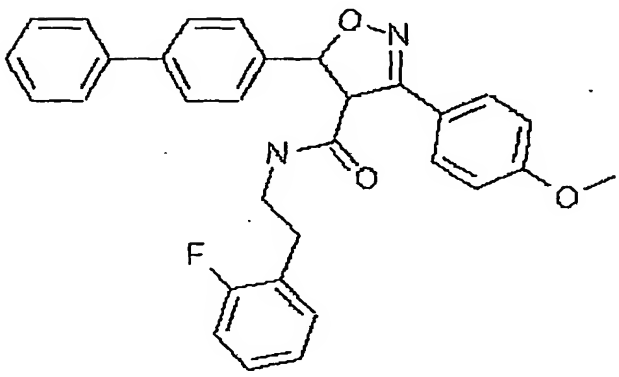


FIG. 15

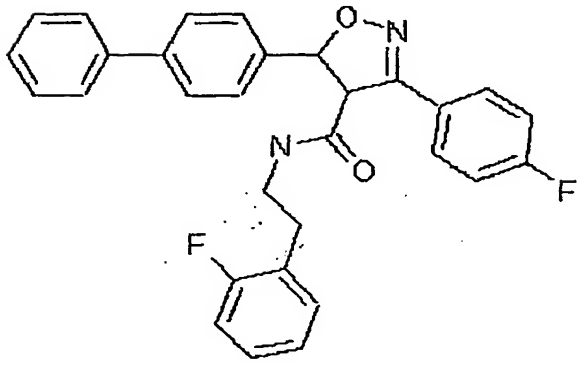


FIG. 16

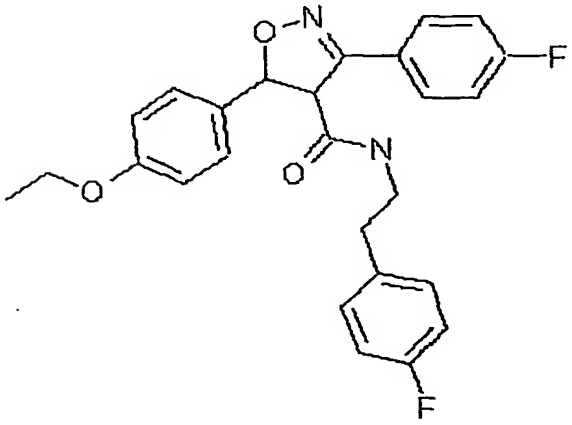


FIG. 17

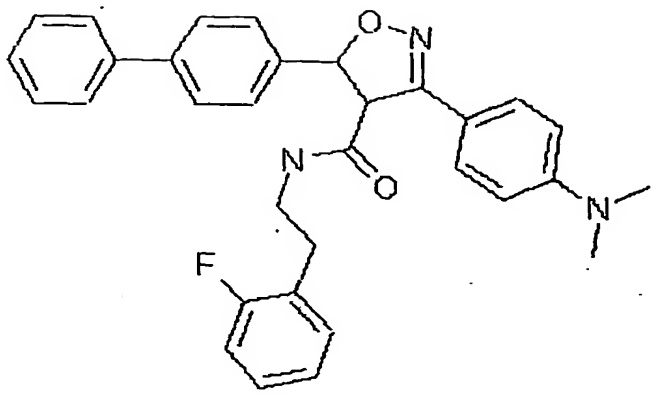


FIG. 18

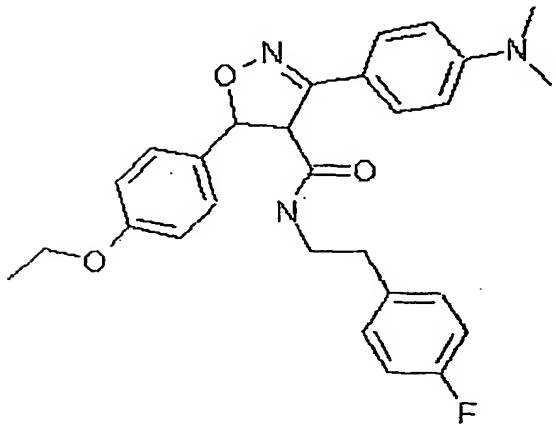


FIG. 19

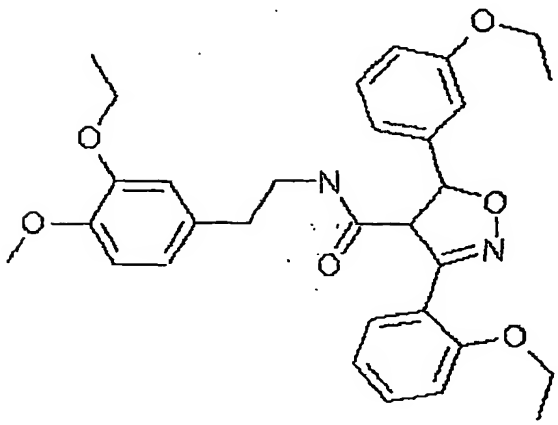


FIG. 20

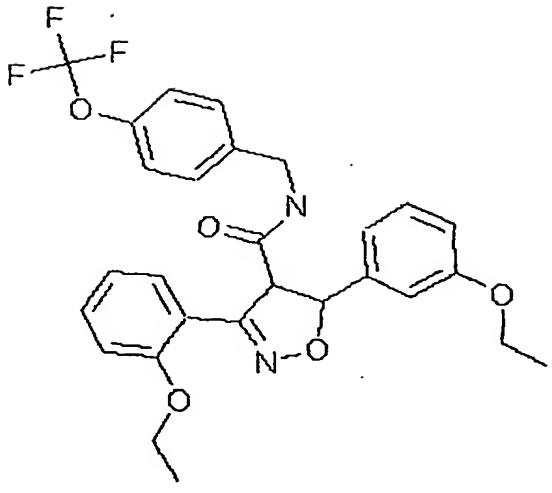


FIG. 21

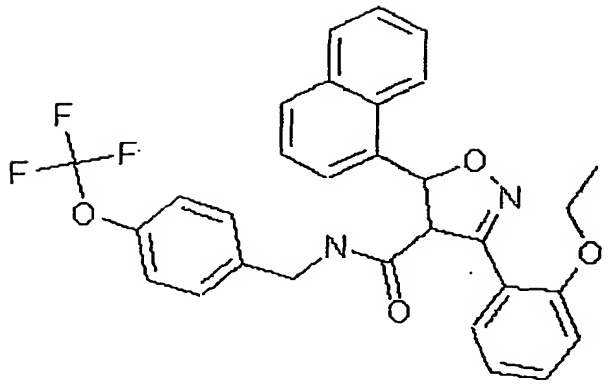


FIG. 22

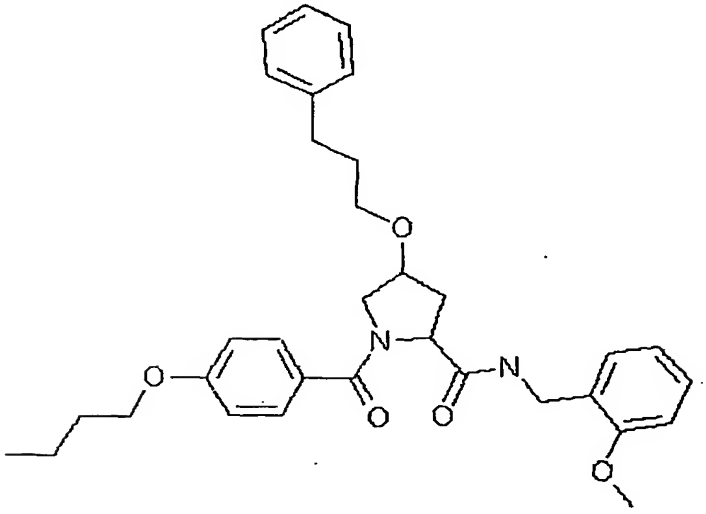


FIG. 23

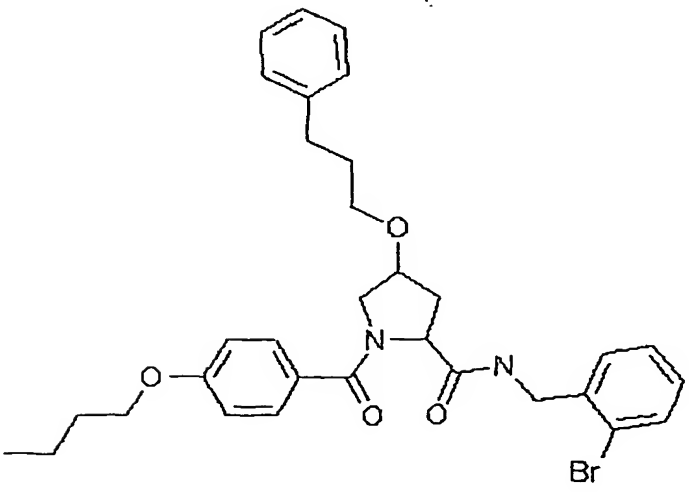


FIG. 24

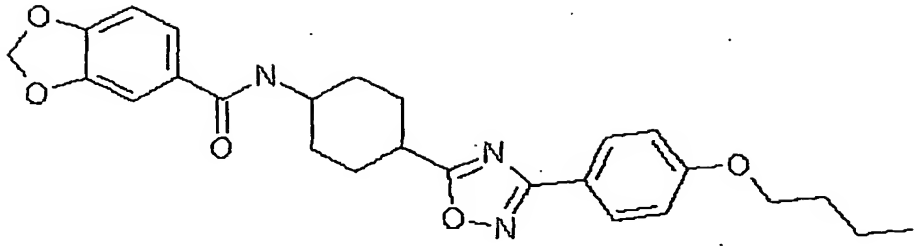


FIG. 25

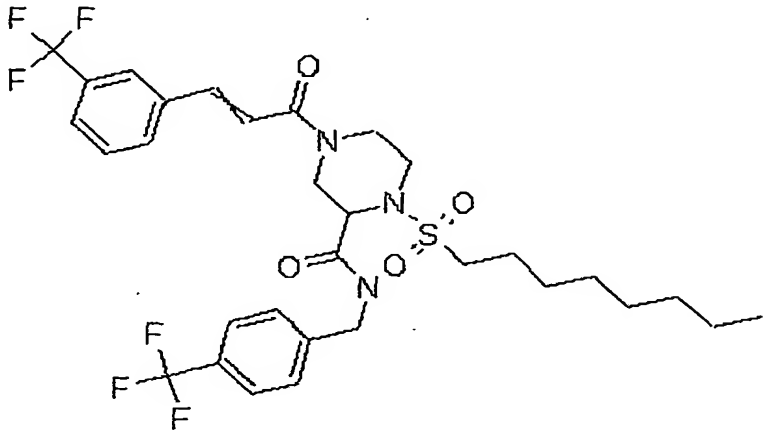


FIG. 26

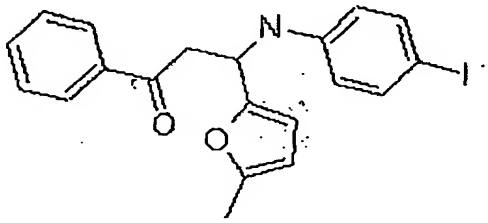


FIG. 27

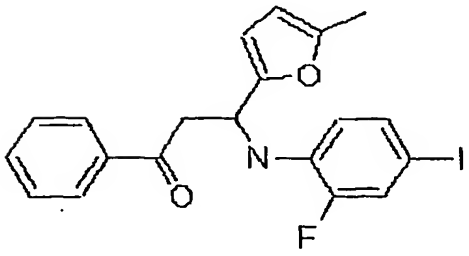


FIG. 28

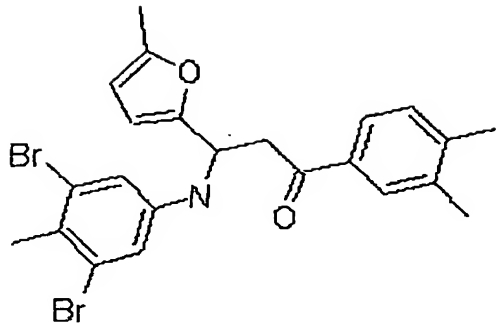


FIG. 29

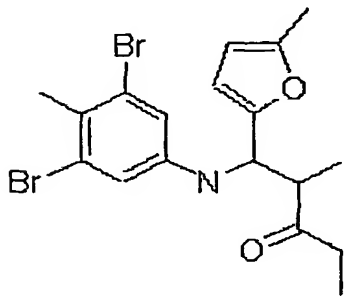


FIG. 30

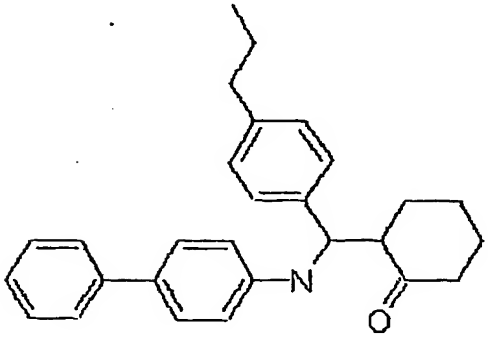


FIG. 31

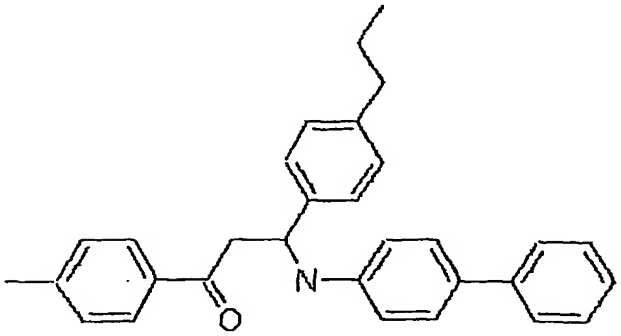


FIG. 32

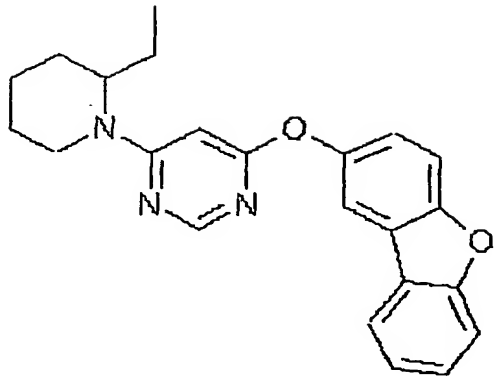


FIG. 33

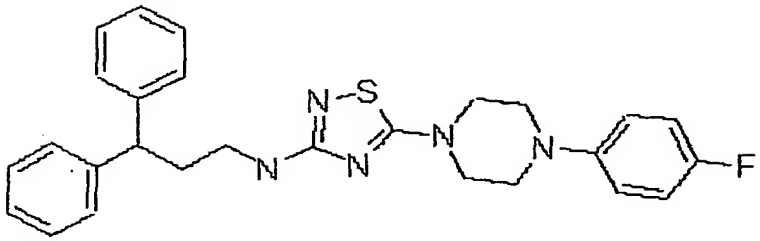


FIG. 34

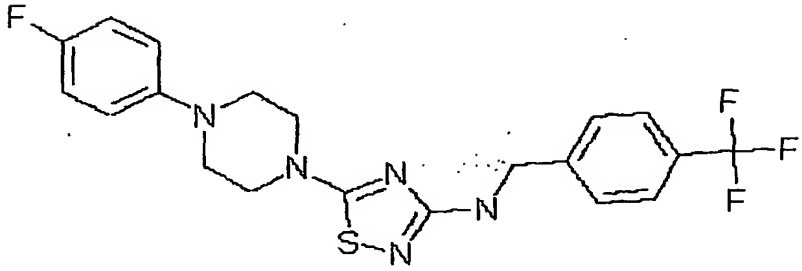


FIG. 35

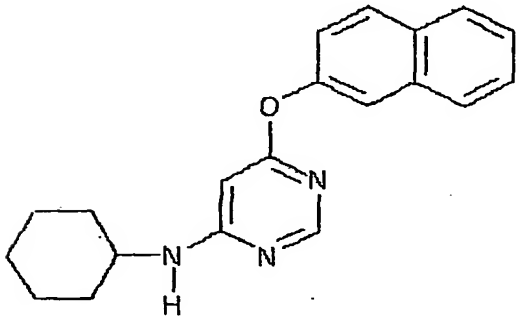


FIG. 36

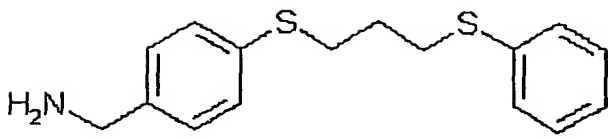


FIG. 37

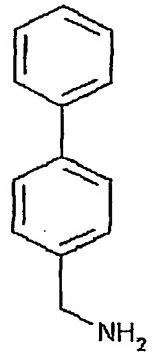


FIG. 38

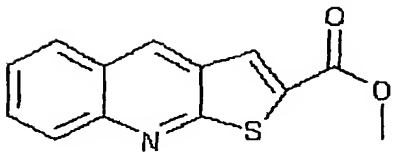


FIG. 39

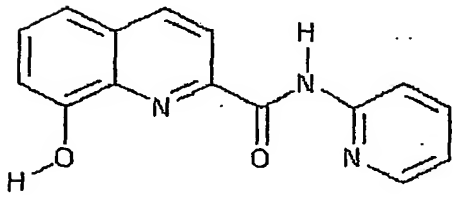


FIG. 40

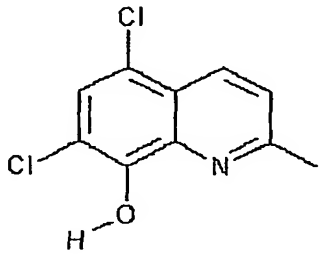


FIG. 41

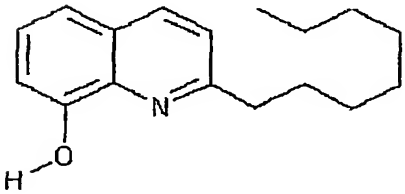


FIG. 42

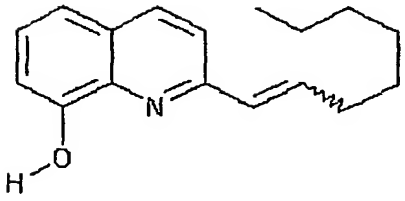


FIG. 43

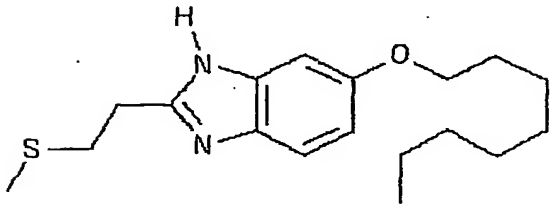


FIG. 44

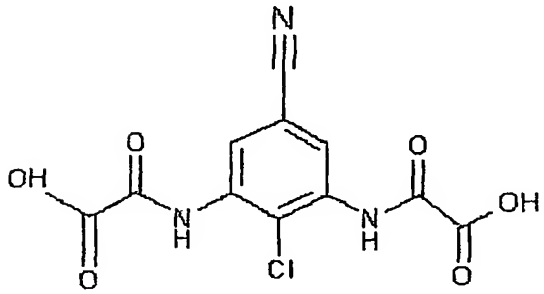


FIG. 45

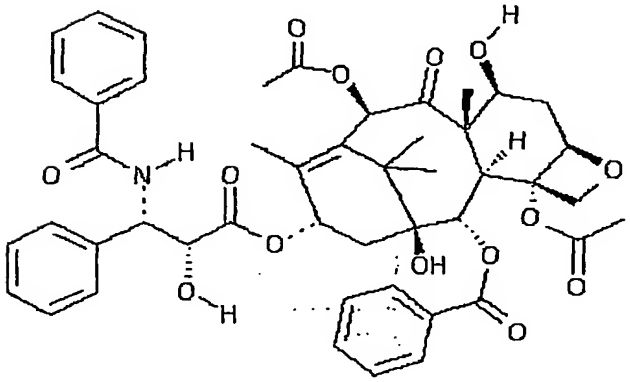


FIG. 46

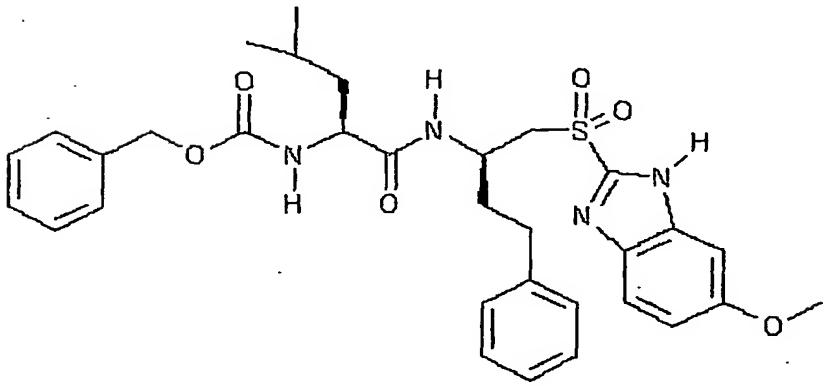


FIG. 47

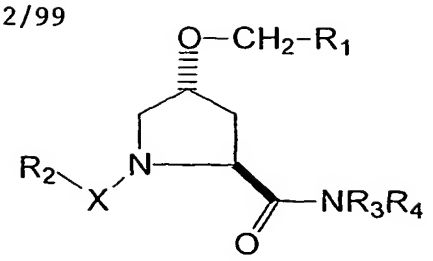


FIG. 48

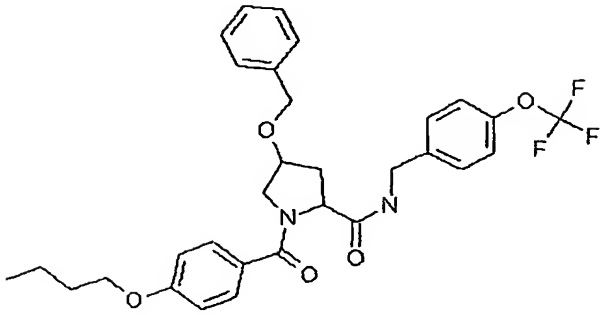


FIG. 49

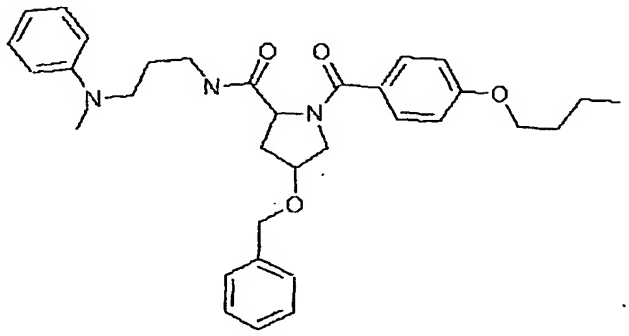


FIG. 50

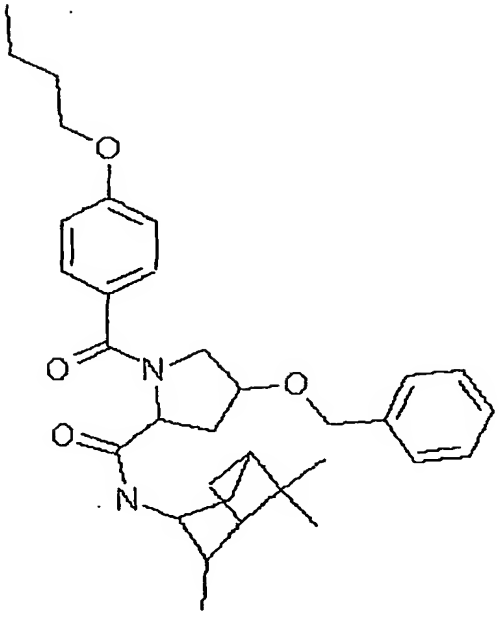


FIG. 51

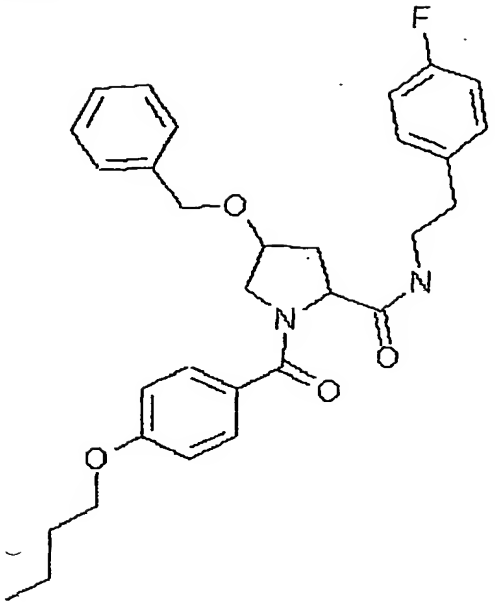


FIG. 52

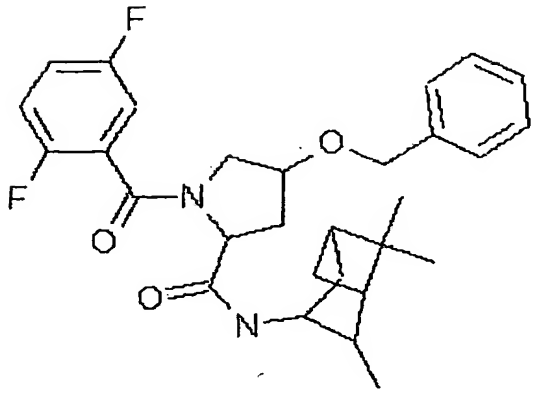


FIG. 53

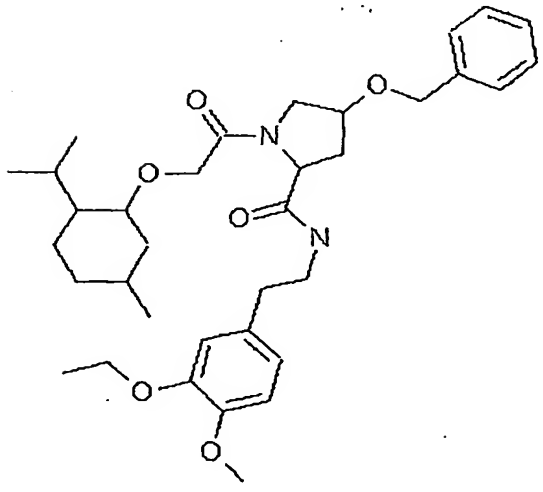


FIG. 54

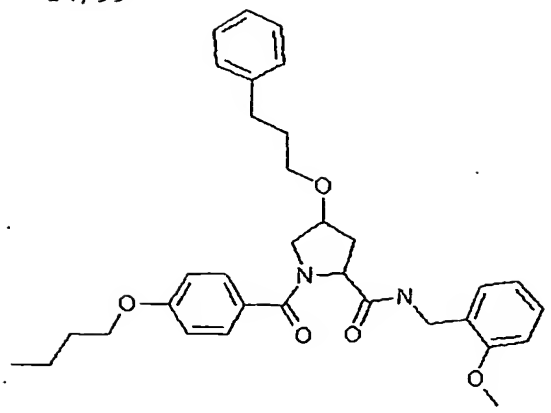


FIG. 55

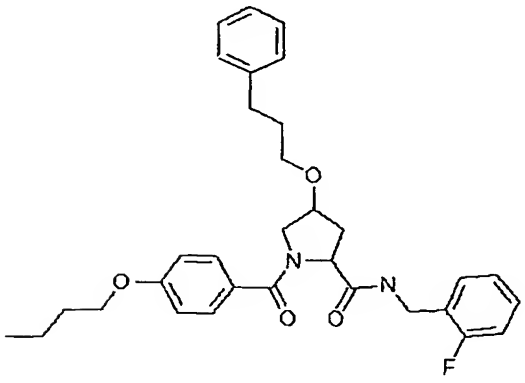


FIG. 56

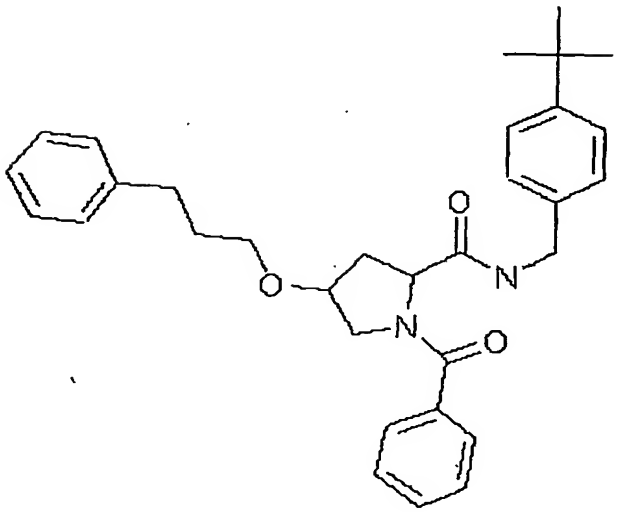


FIG. 57

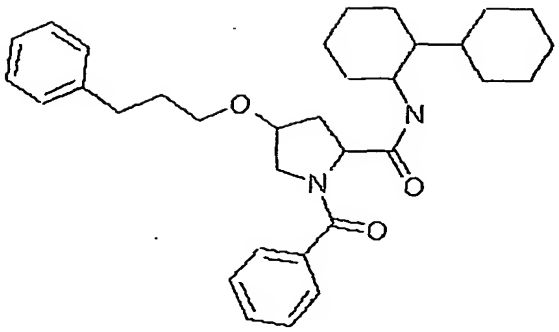


FIG. 58

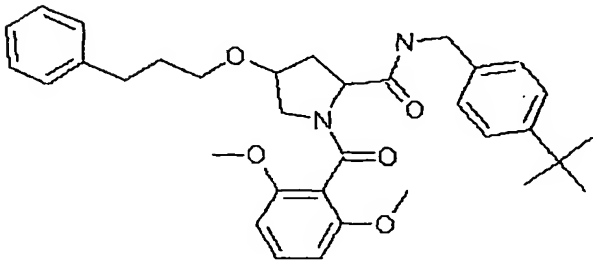


FIG. 59

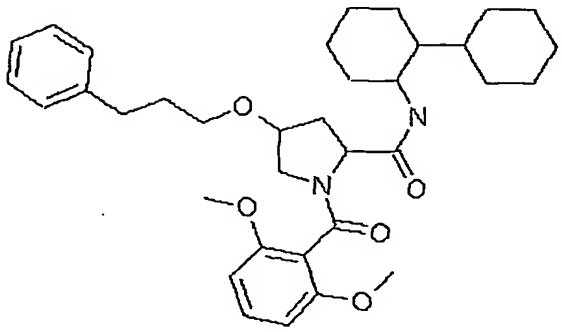


FIG. 60

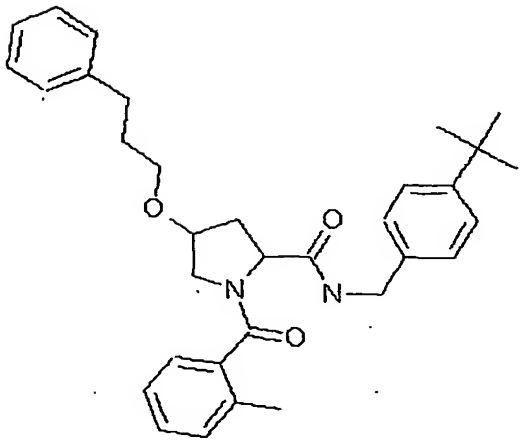


FIG. 61

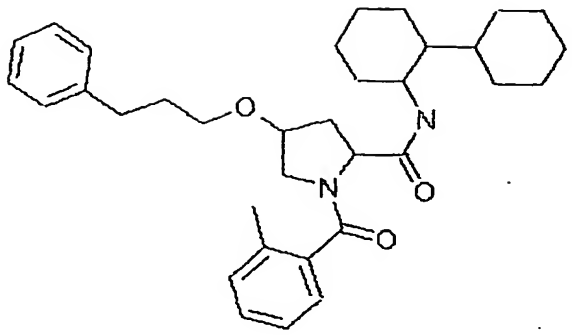


FIG. 62

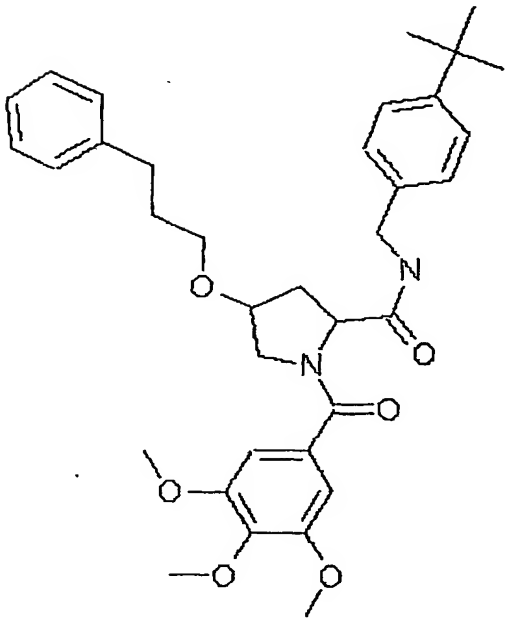


FIG. 63

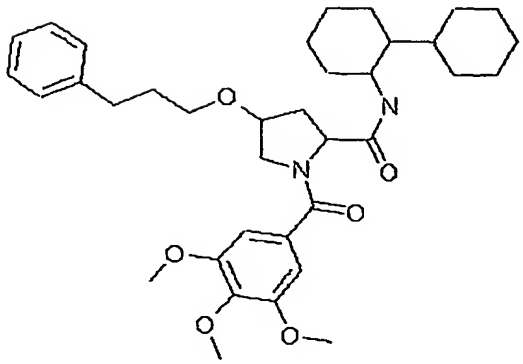


FIG. 64

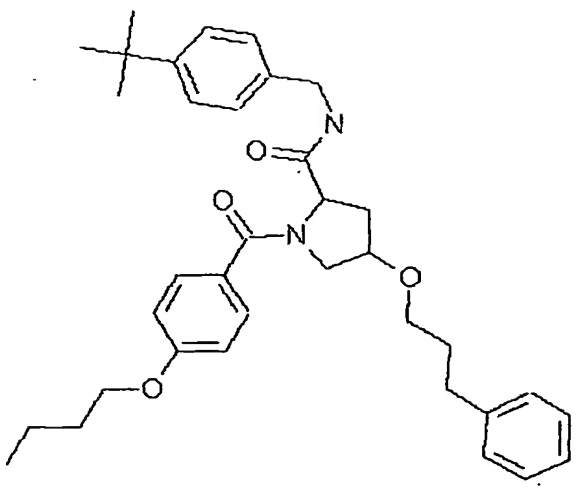


FIG. 65

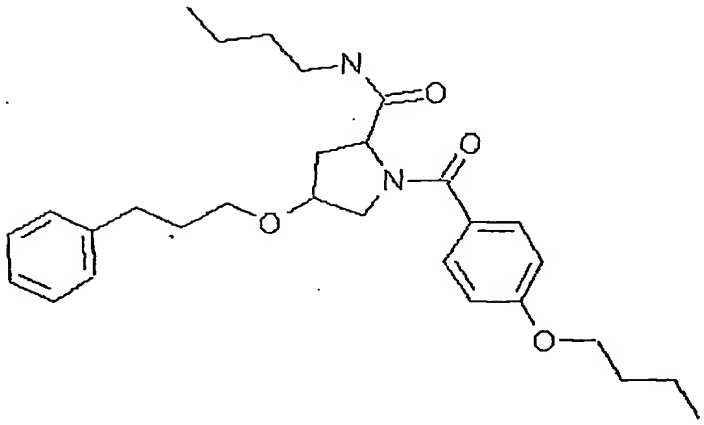


FIG. 66

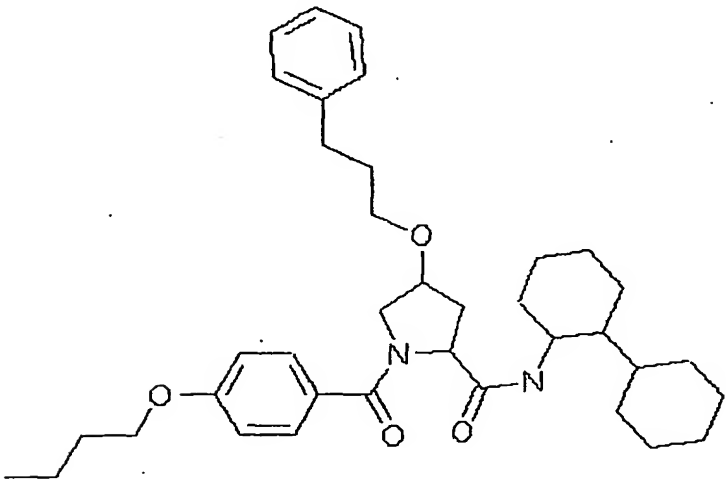


FIG. 67

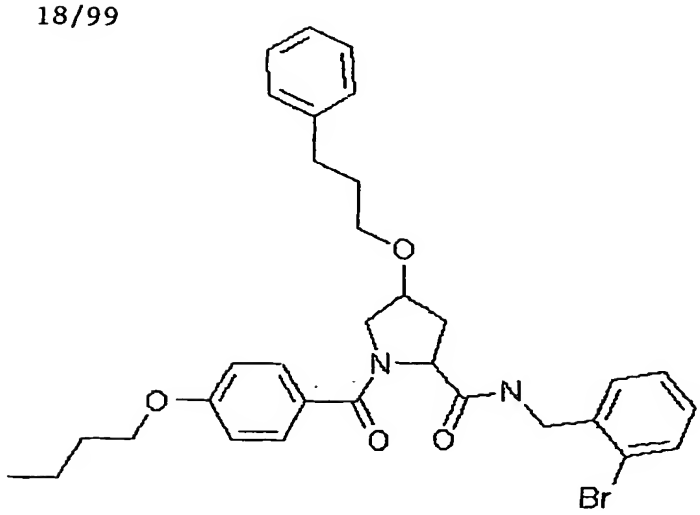


FIG. 68

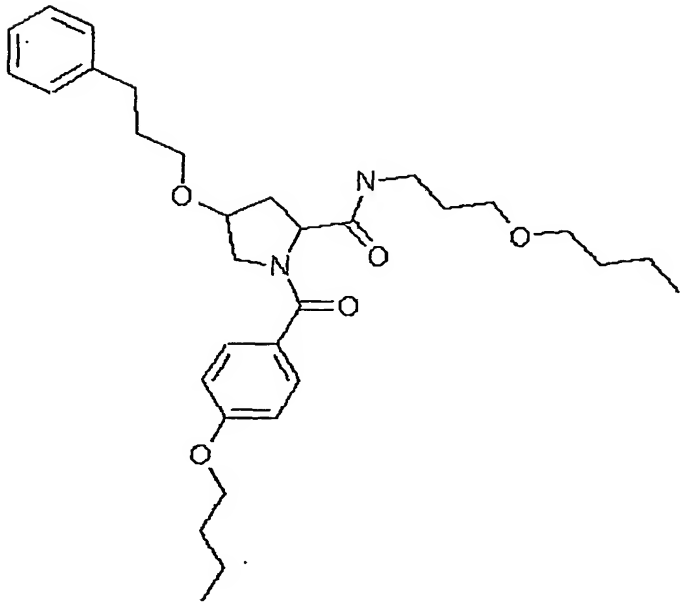


FIG. 69

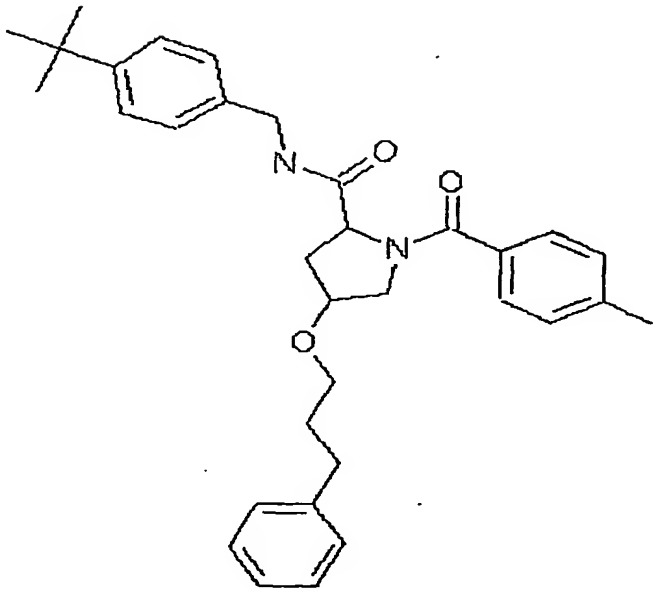


FIG. 70

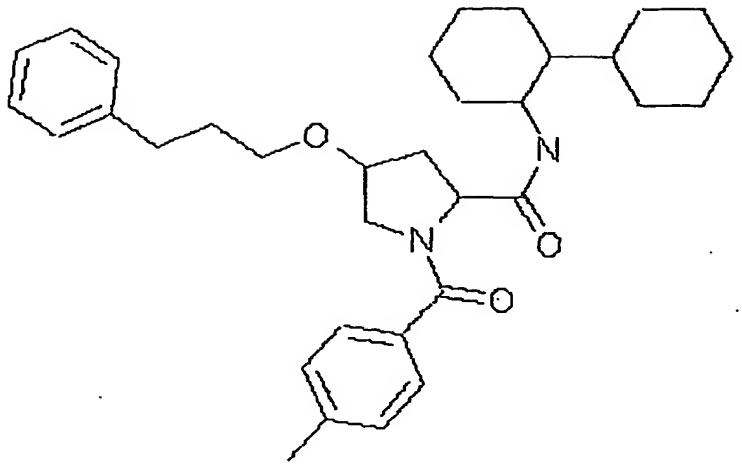


FIG. 71

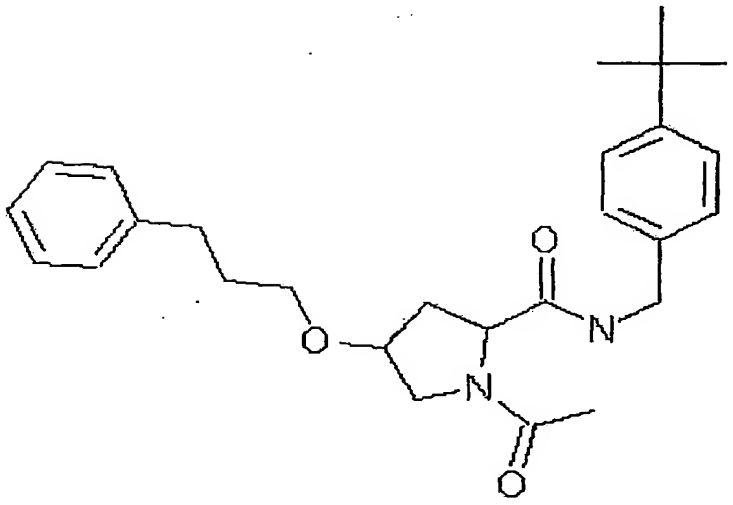


FIG. 72

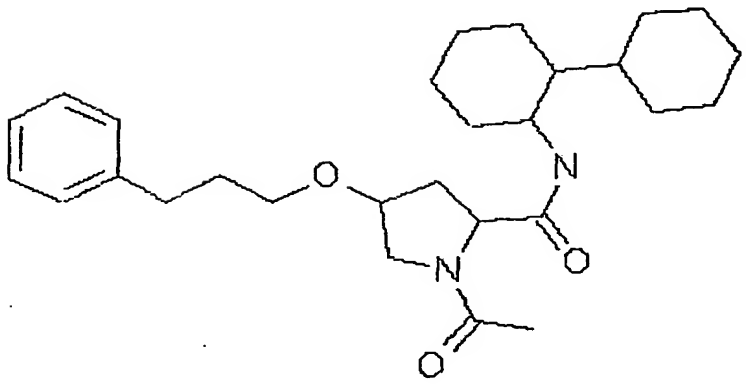


FIG. 73

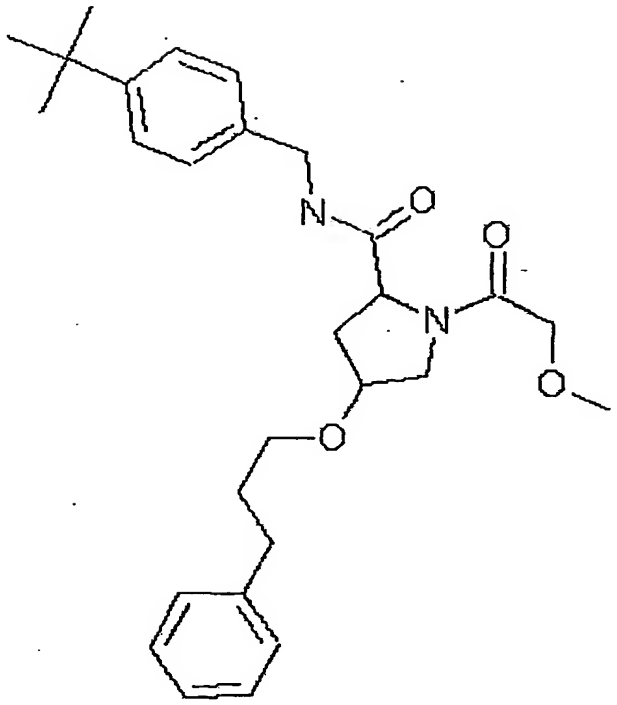


FIG. 74

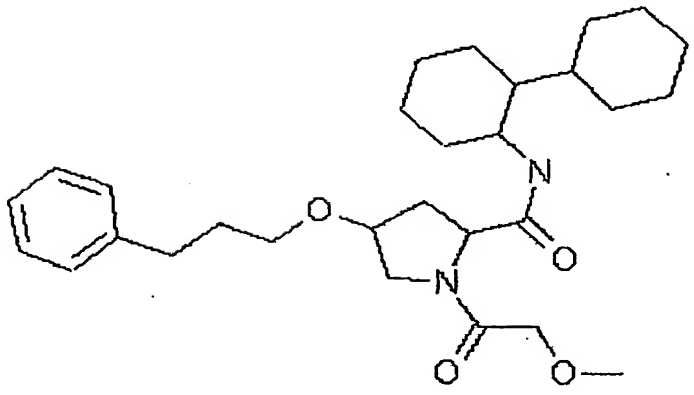


FIG. 75

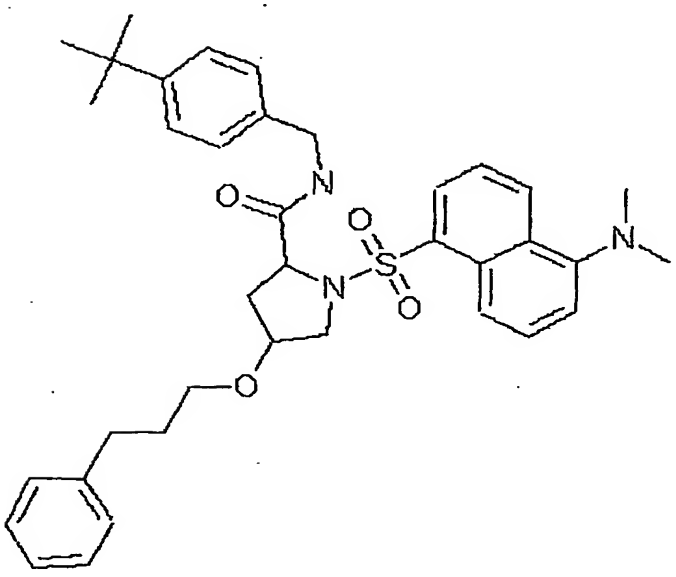


FIG. 76

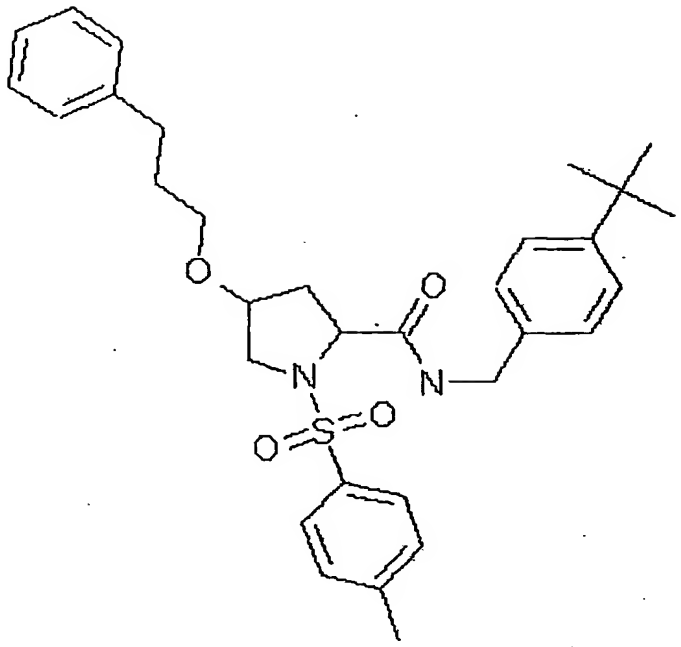


FIG. 77

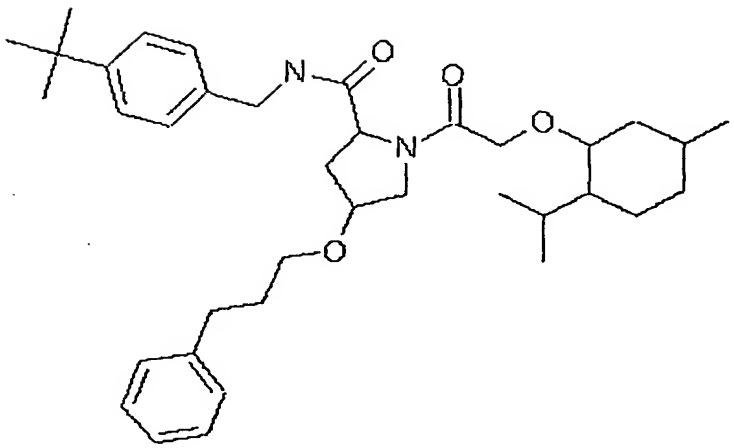


FIG. 78

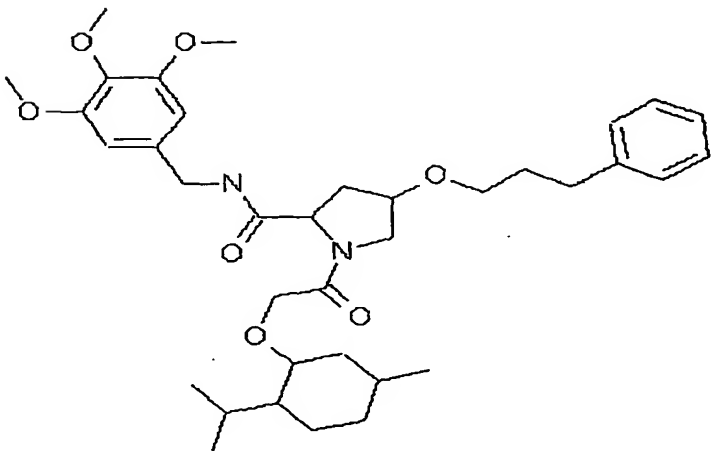


FIG. 79

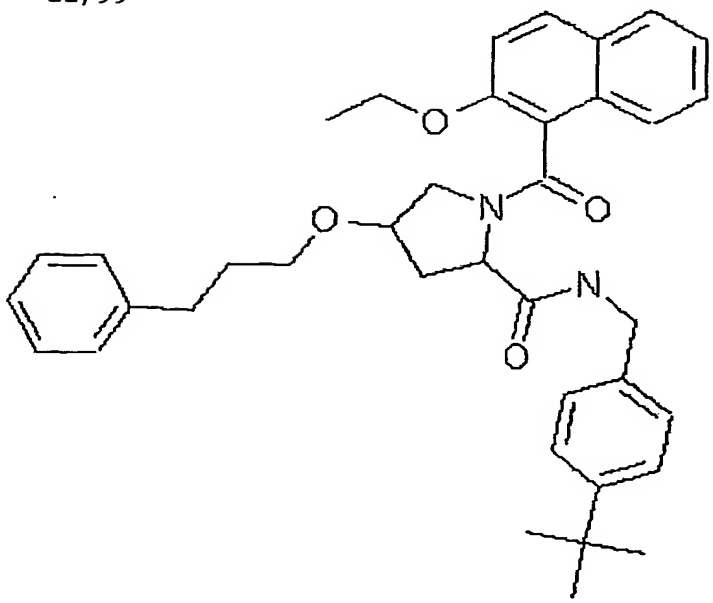


FIG. 80

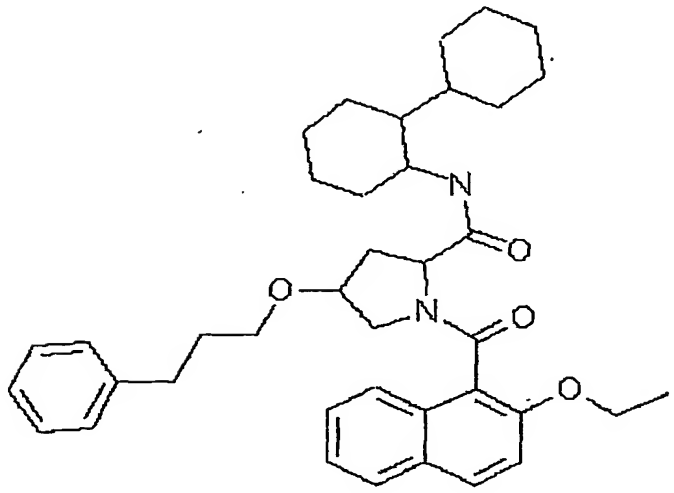


FIG. 81

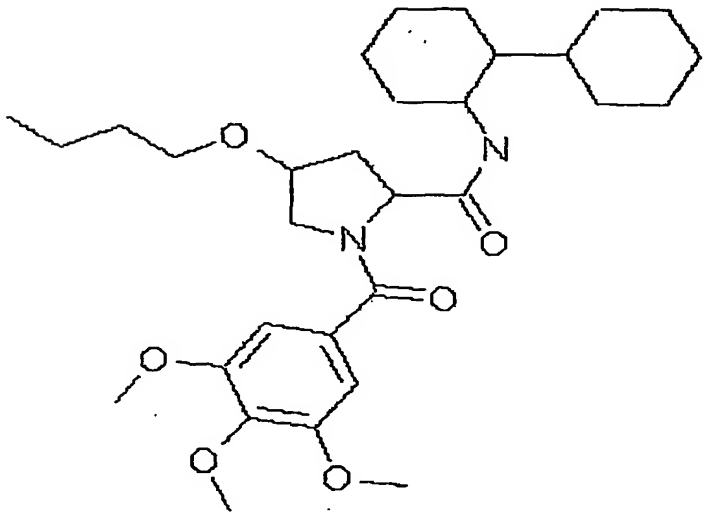


FIG. 82

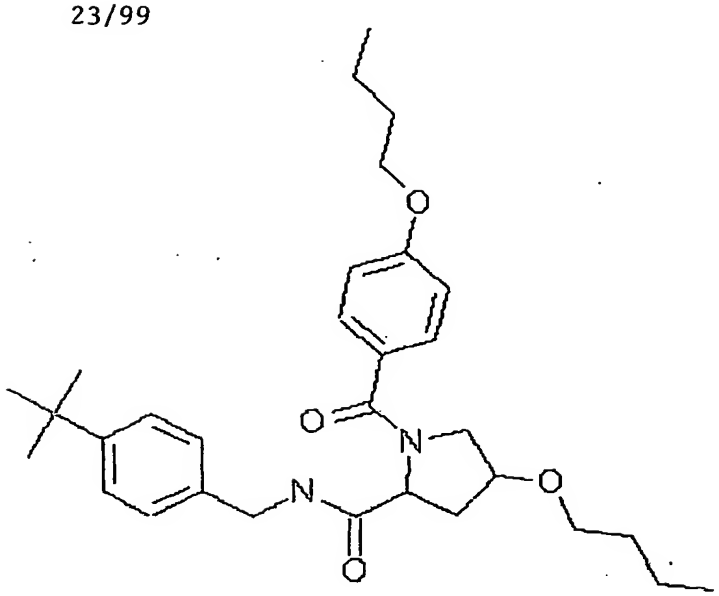


FIG. 83

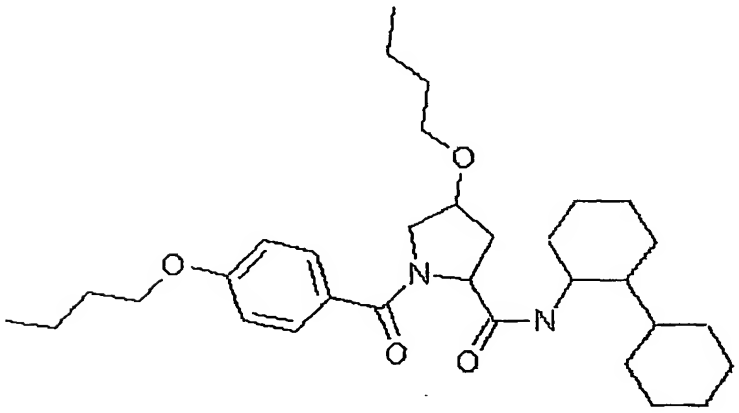


FIG. 84

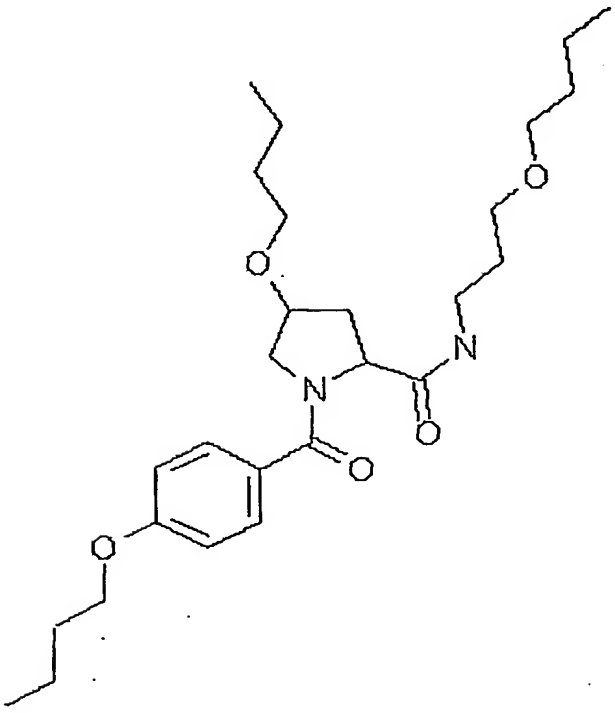


FIG. 85

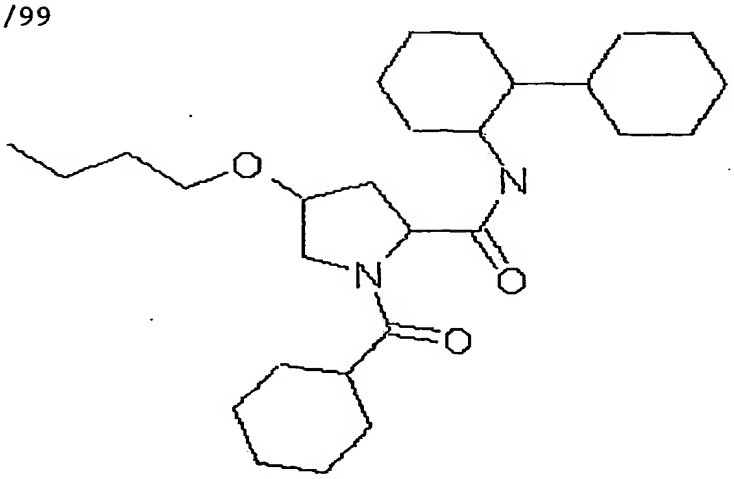


FIG. 86

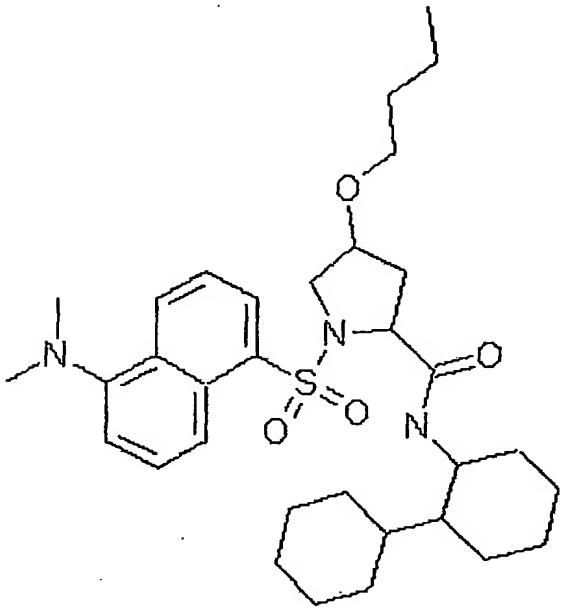


FIG. 87

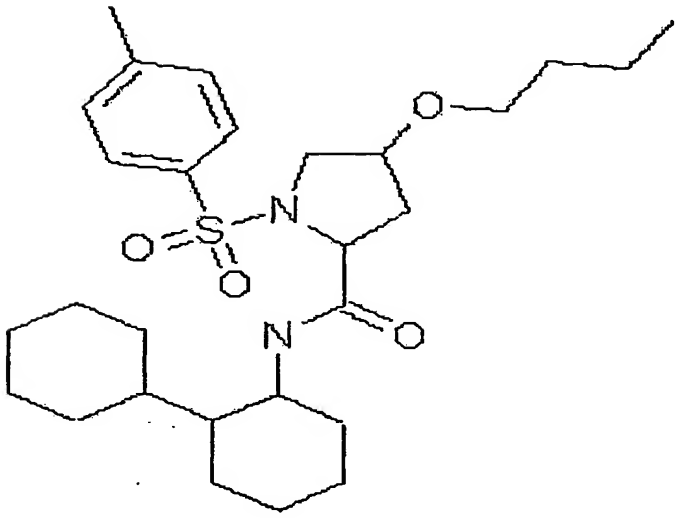


FIG. 88

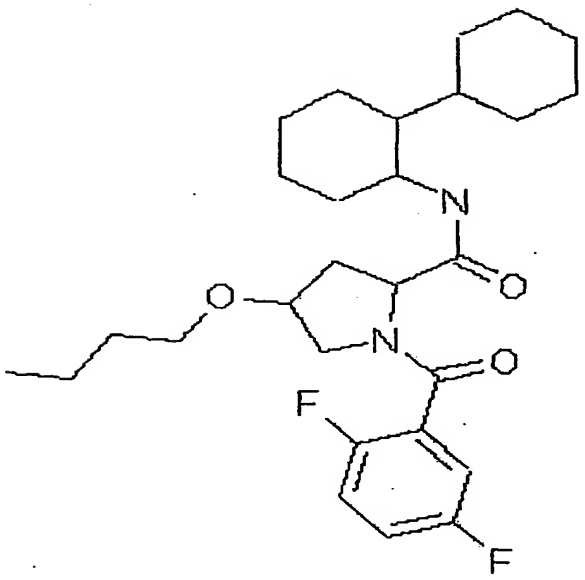


FIG. 89

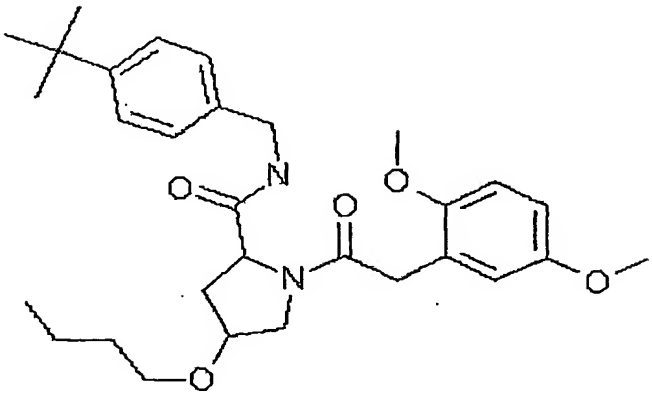


FIG. 90

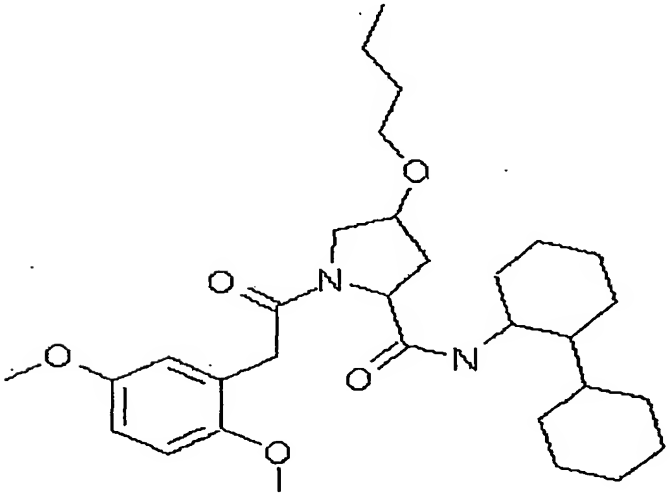


FIG. 91

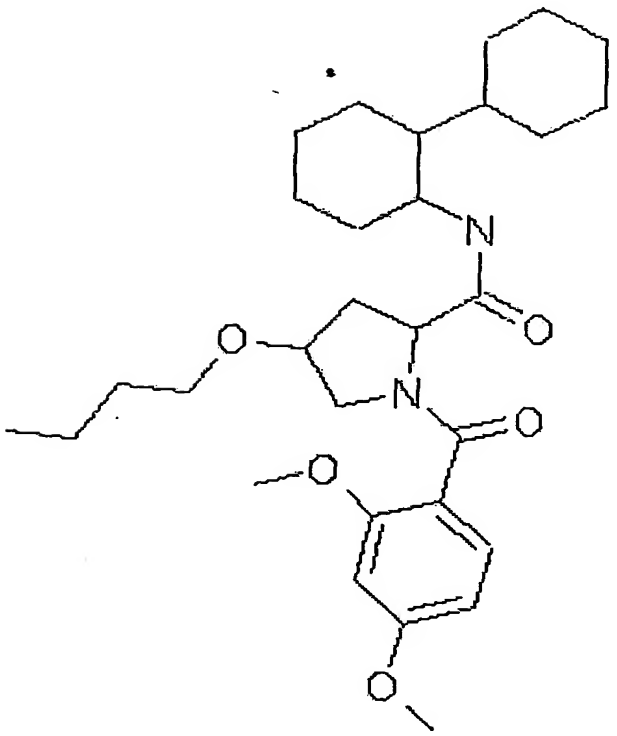


FIG. 92

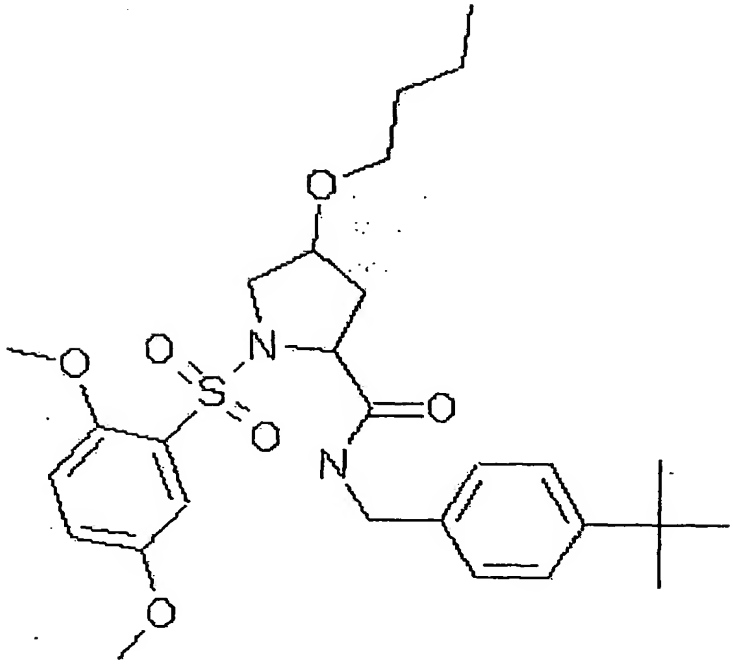


FIG. 93

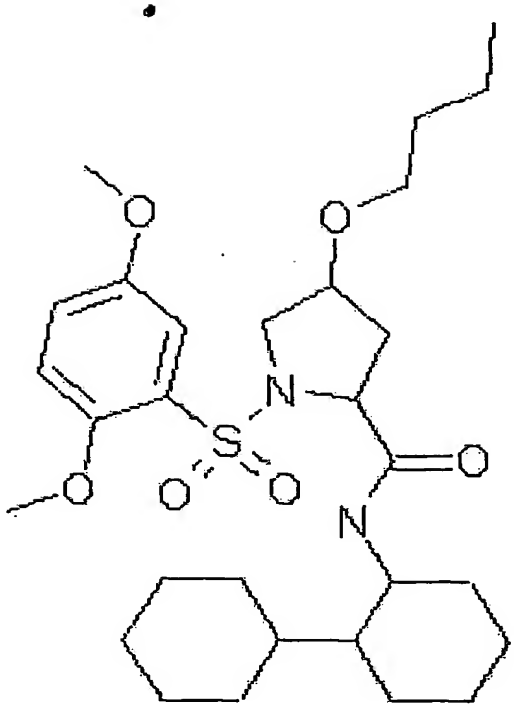


FIG. 94

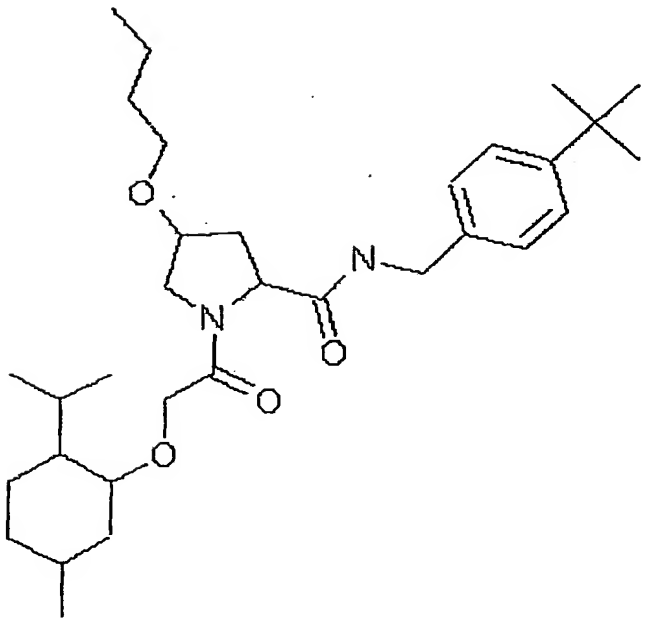


FIG. 95

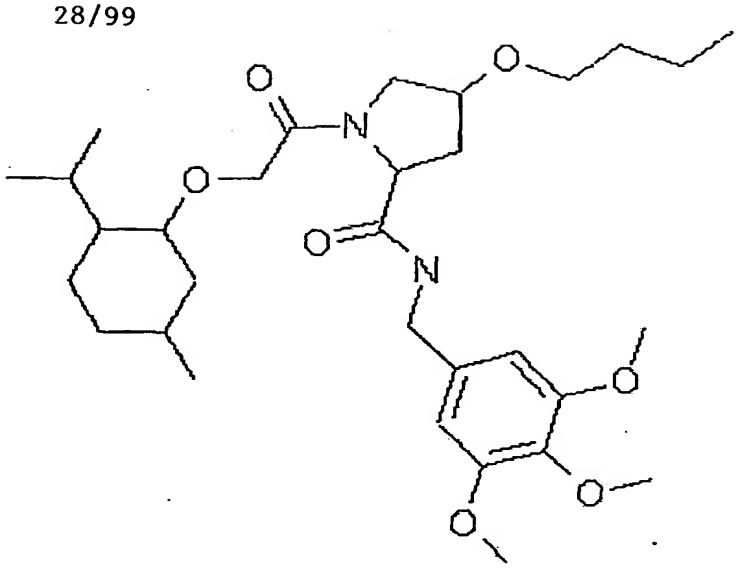


FIG. 96

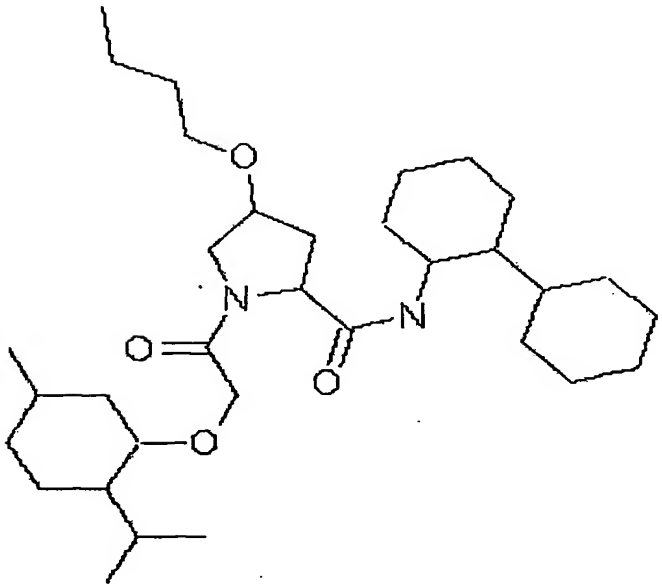


FIG. 97

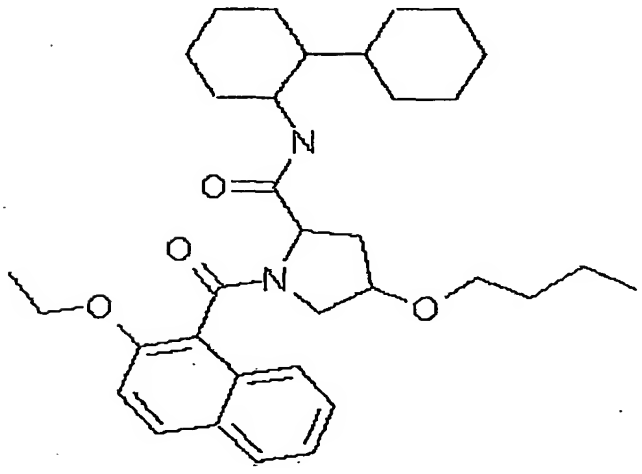


FIG. 98

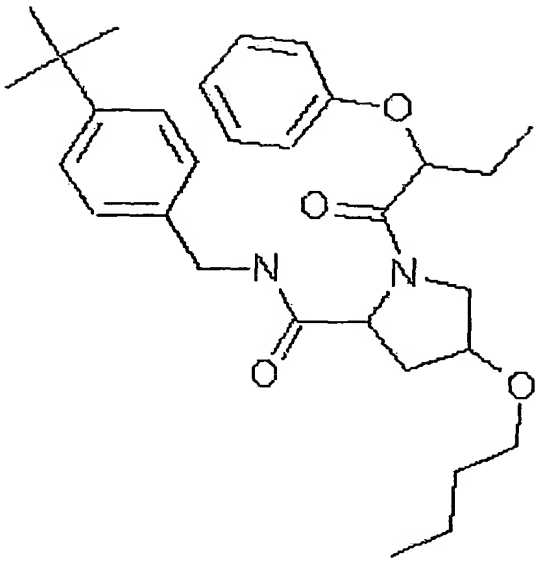


FIG. 99

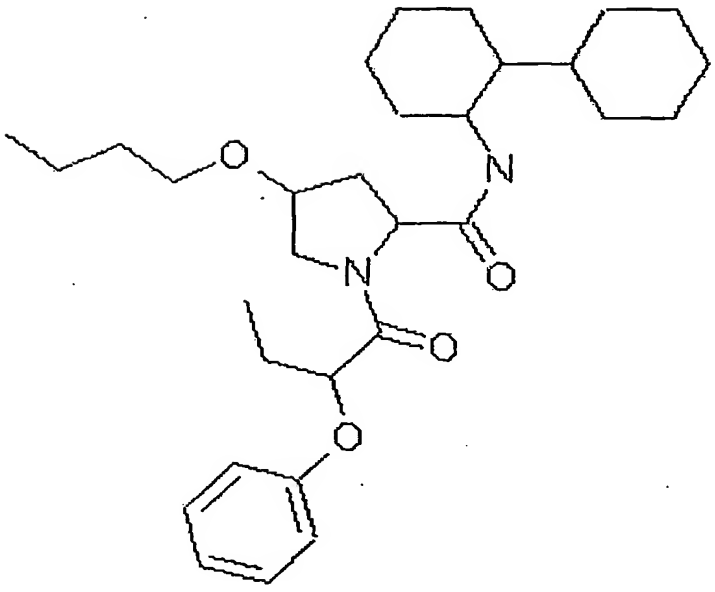


FIG. 100

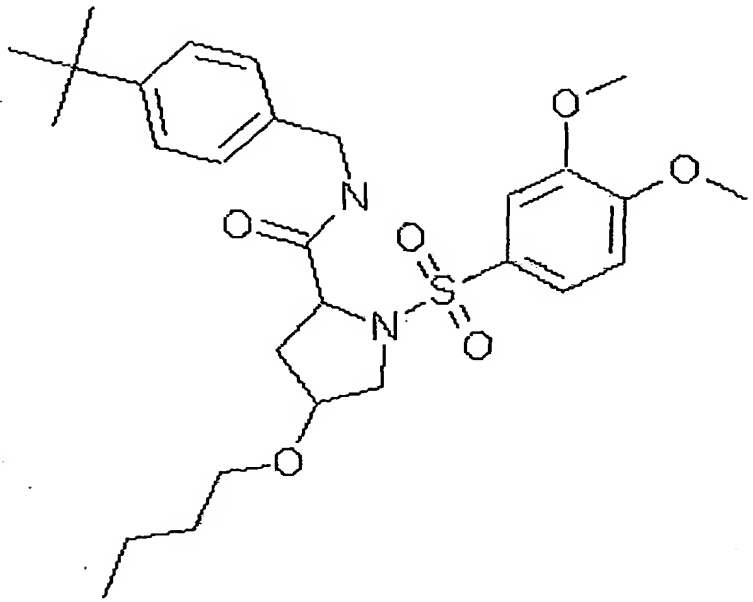


FIG. 101

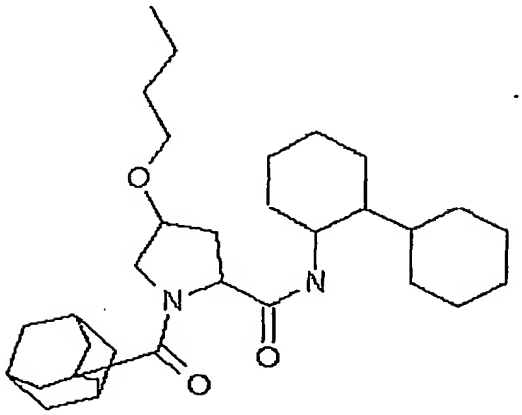


FIG. 102

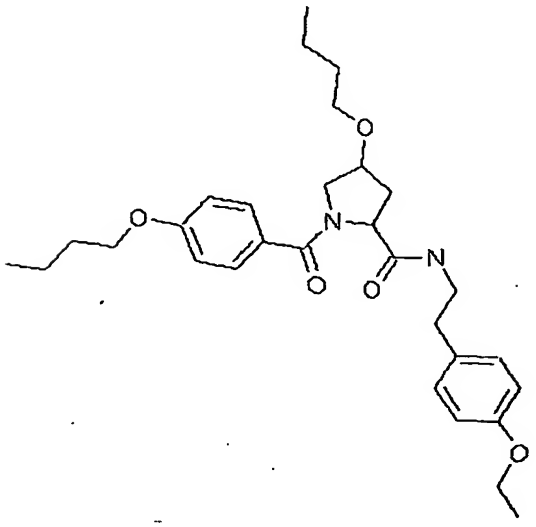


FIG. 103

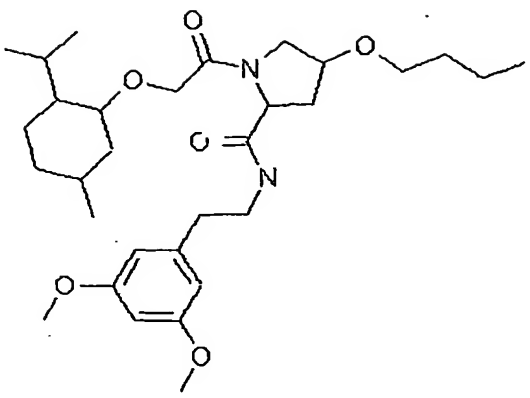


FIG. 104

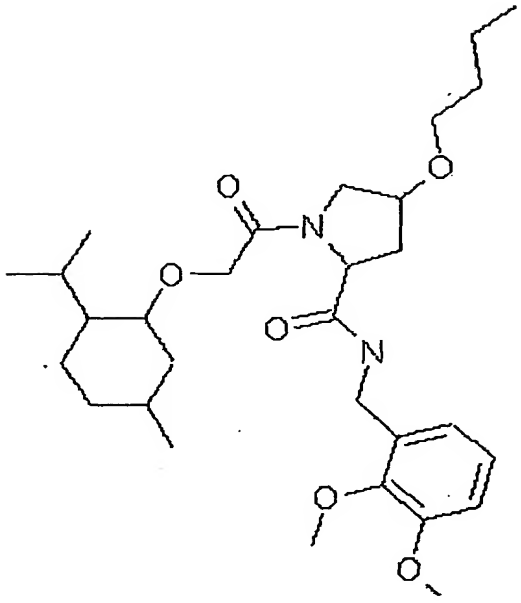


FIG. 105

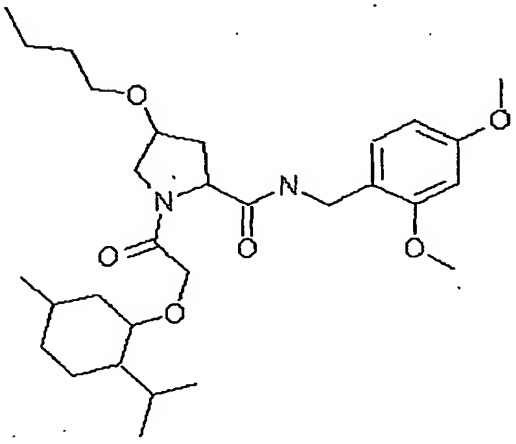


FIG. 106

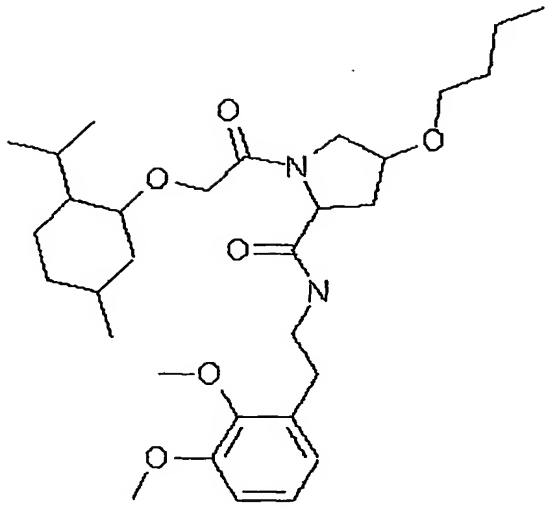


FIG. 107

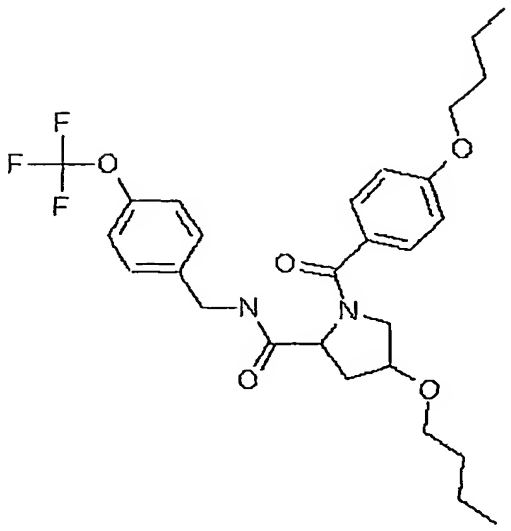


FIG. 108

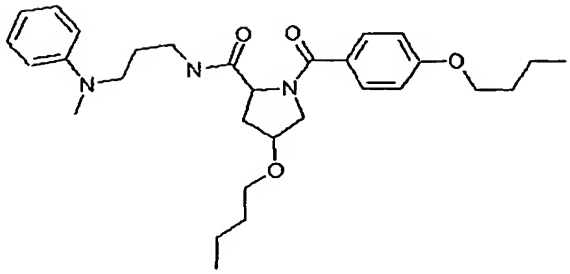


FIG. 109

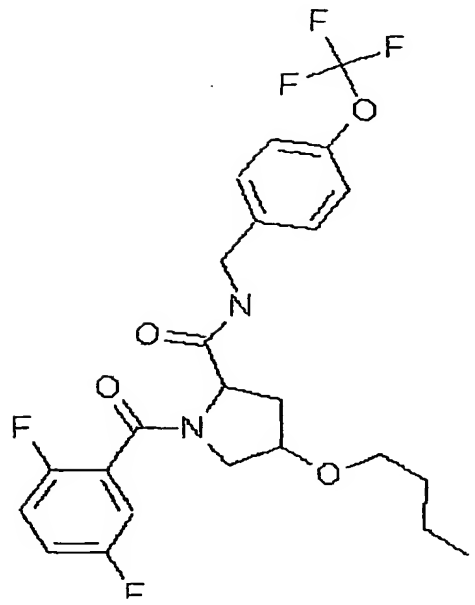


FIG. 110

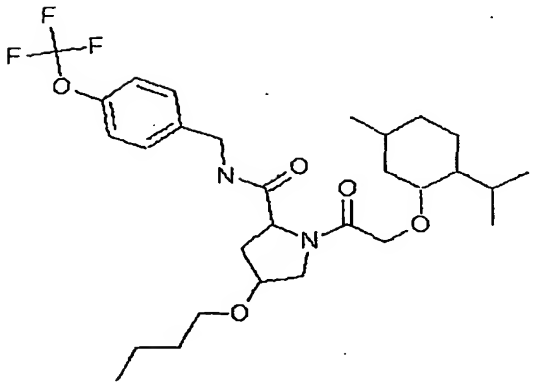


FIG. 111

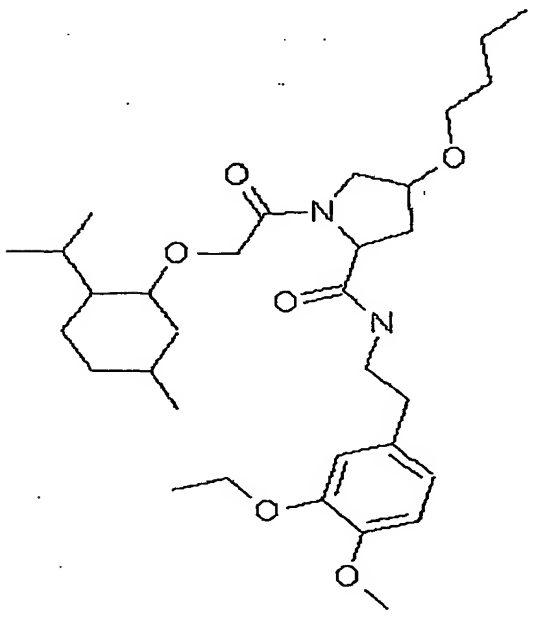


FIG. 112

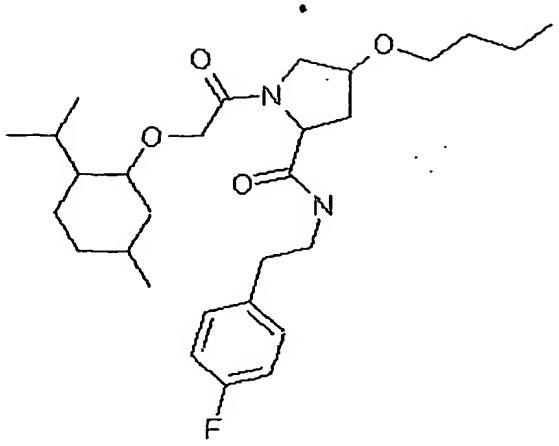


FIG. 113

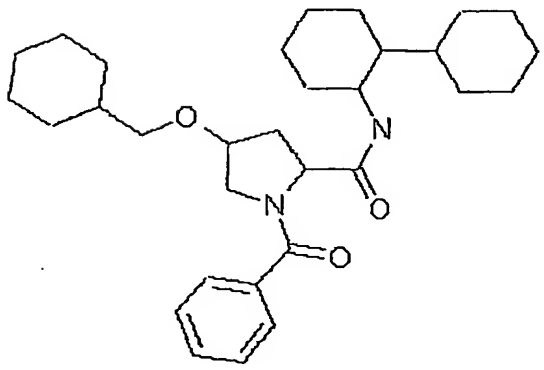


FIG. 114

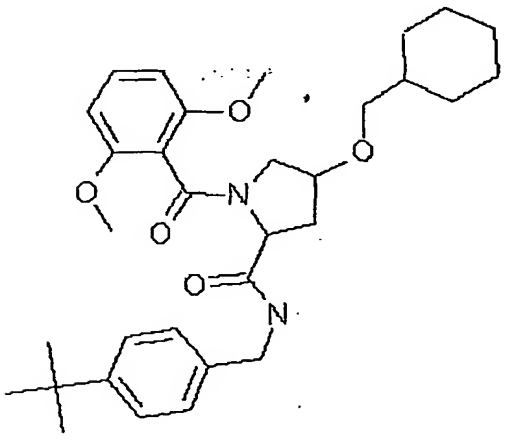


FIG. 115

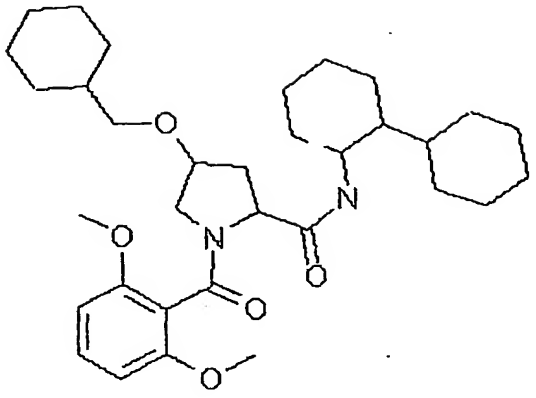


FIG. 116

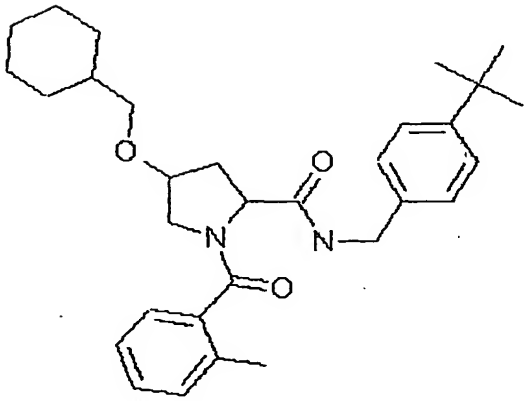


FIG. 117

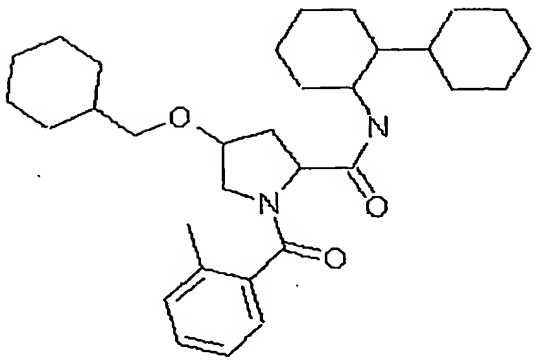


FIG. 118

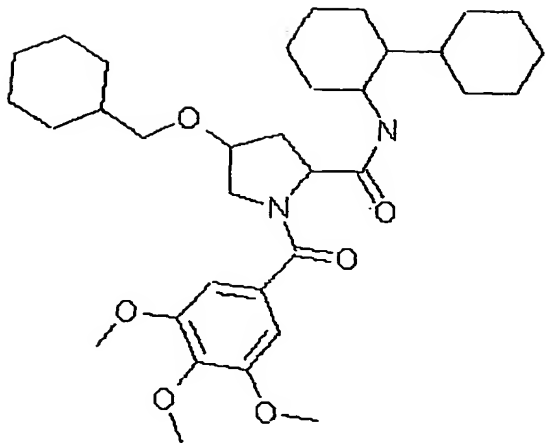


FIG. 119

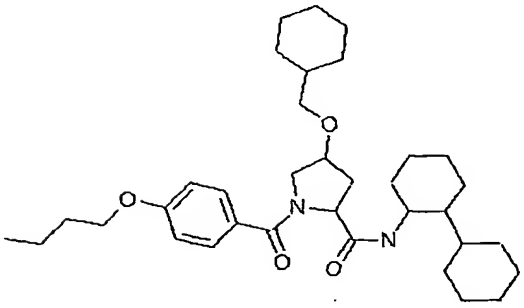


FIG. 120

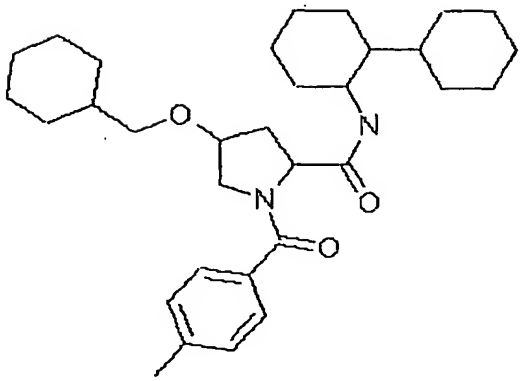


FIG. 121

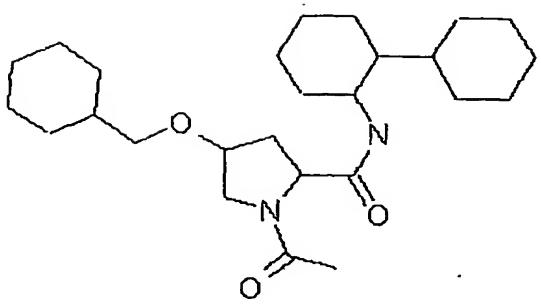


FIG. 122

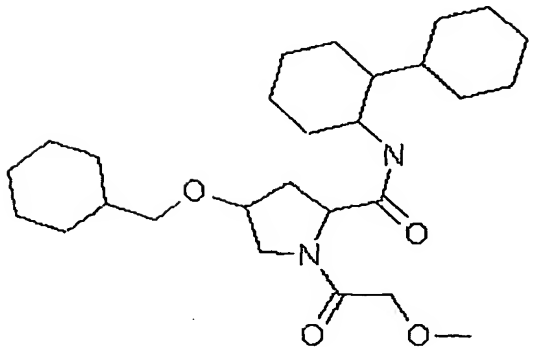


FIG. 123

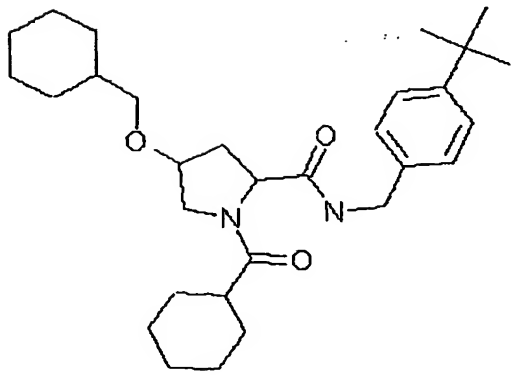


FIG. 124

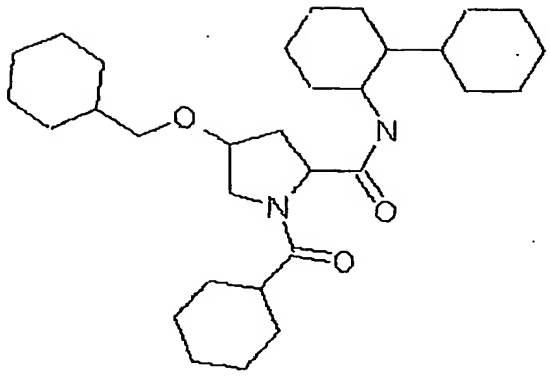


FIG. 125

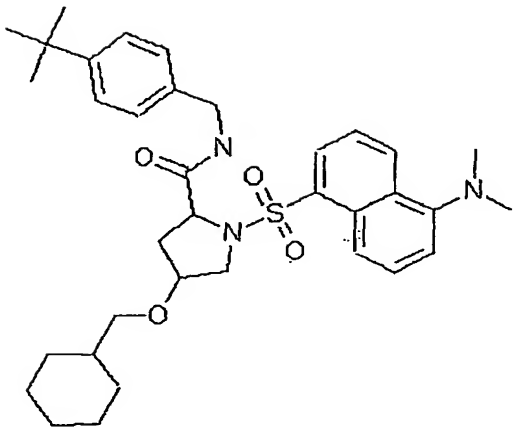


FIG. 126

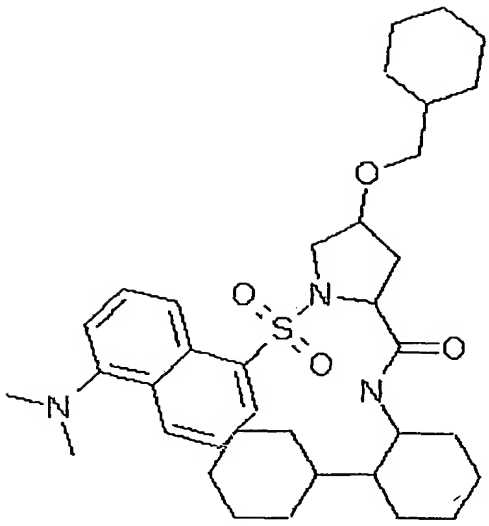


FIG. 127

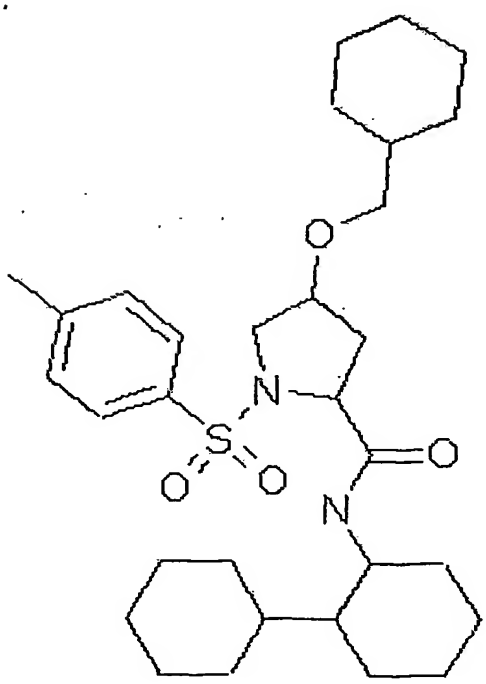


FIG. 128

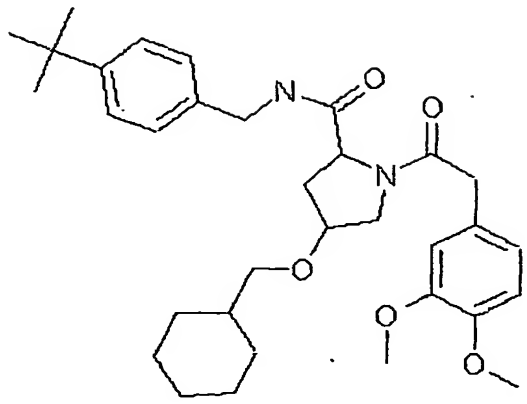


FIG. 129

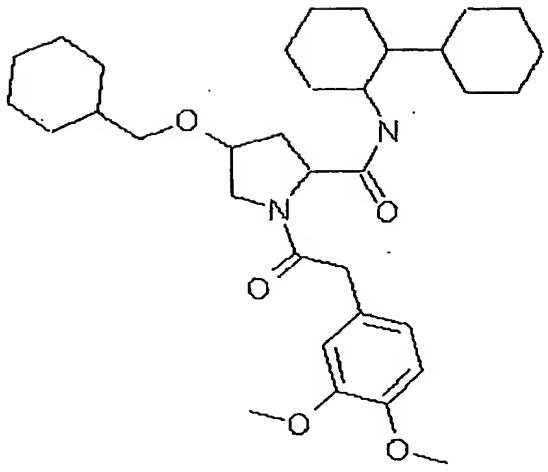


FIG. 130

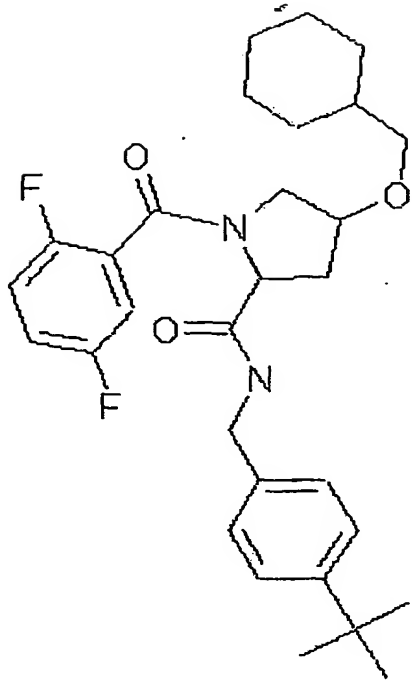


FIG. 131

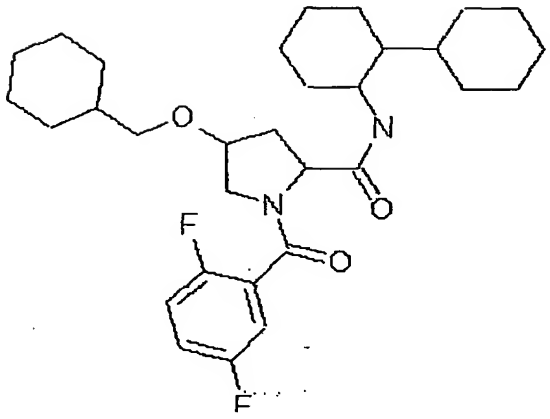


FIG. 132

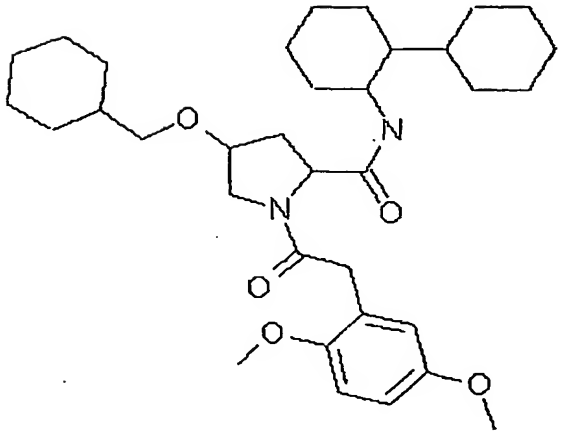


FIG. 133

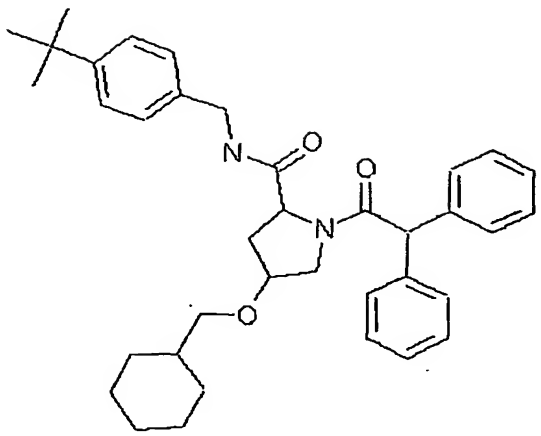


FIG. 134

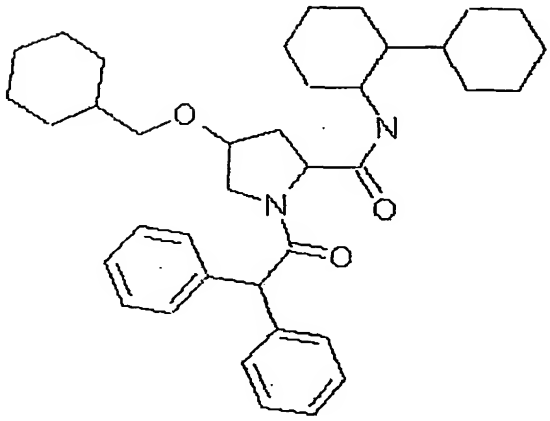


FIG. 135

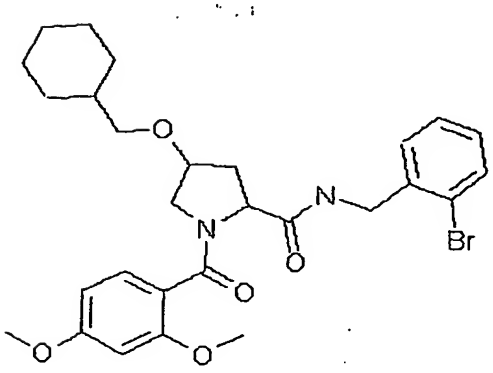


FIG. 136

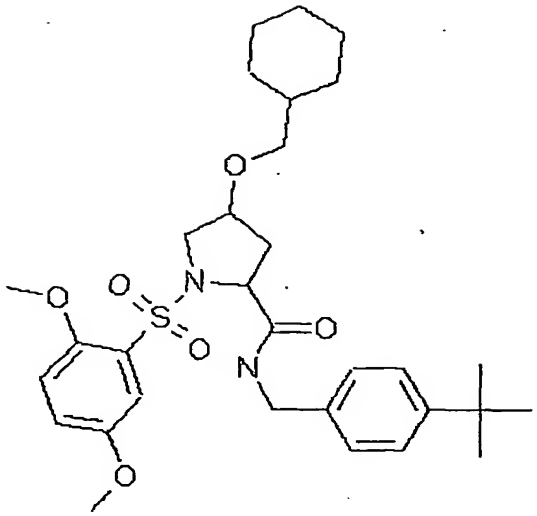


FIG. 137

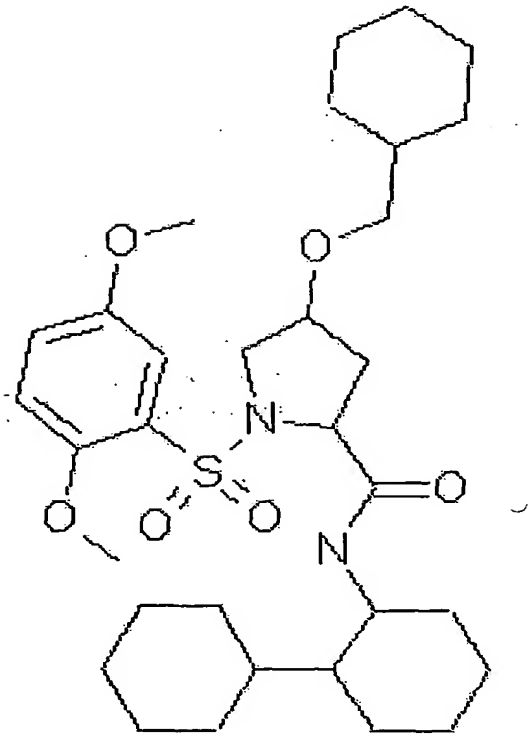


FIG. 138

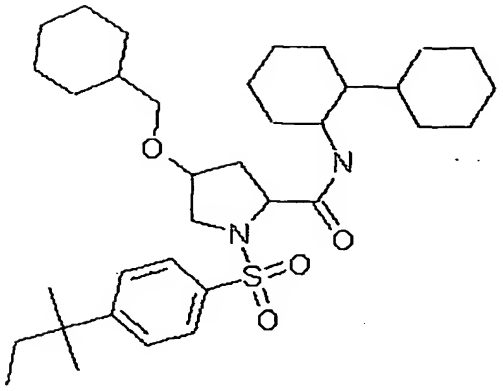


FIG. 139

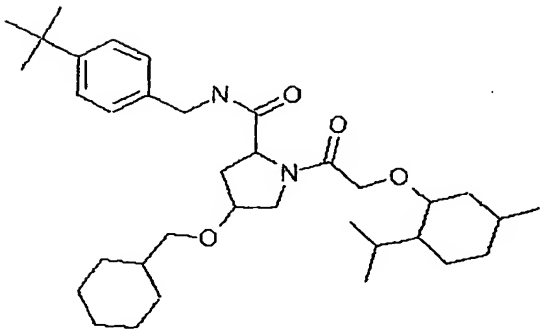


FIG. 140

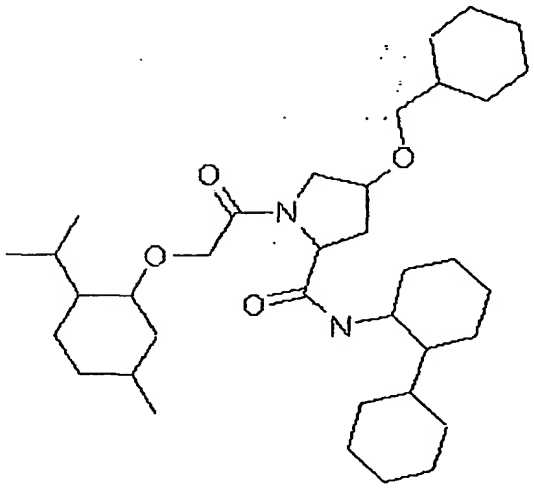


FIG. 141

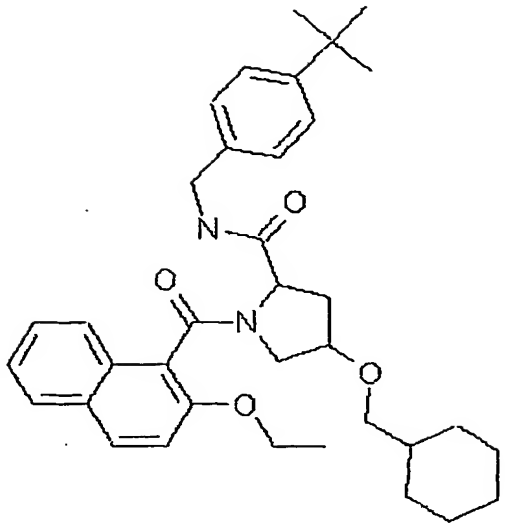


FIG. 142

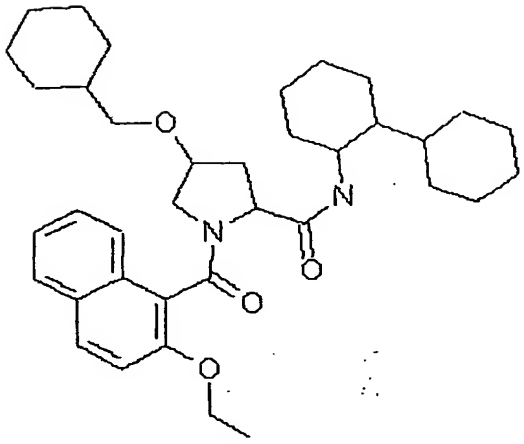


FIG. 143

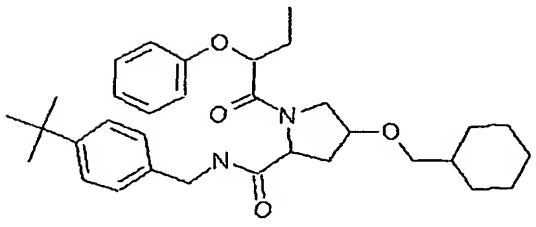


FIG. 144

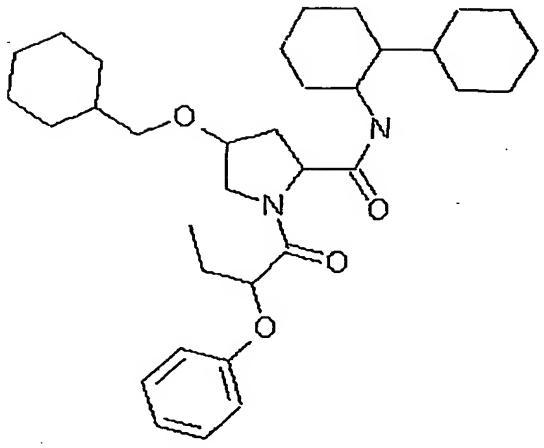


FIG. 145

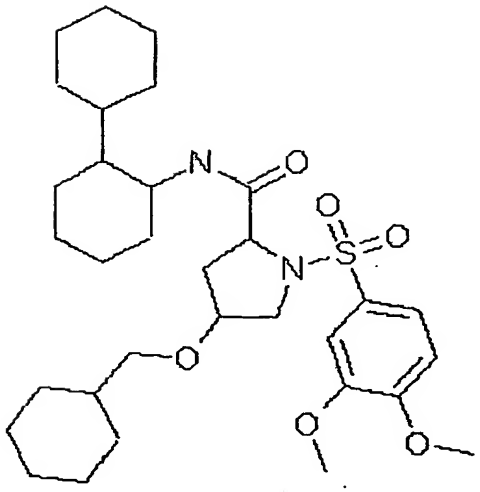


FIG. 146

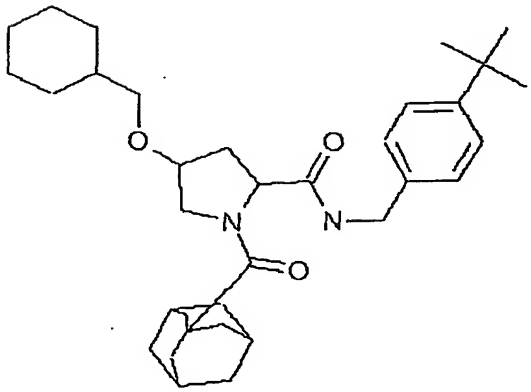


FIG. 147

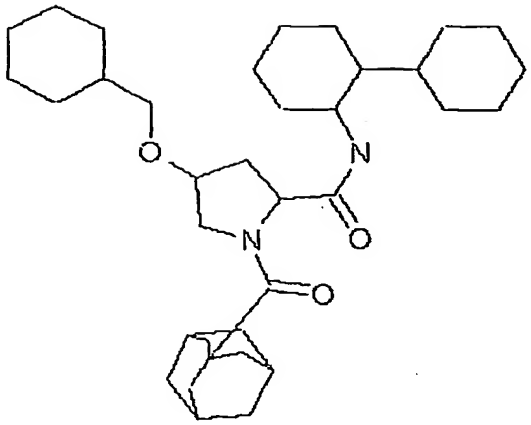


FIG. 148

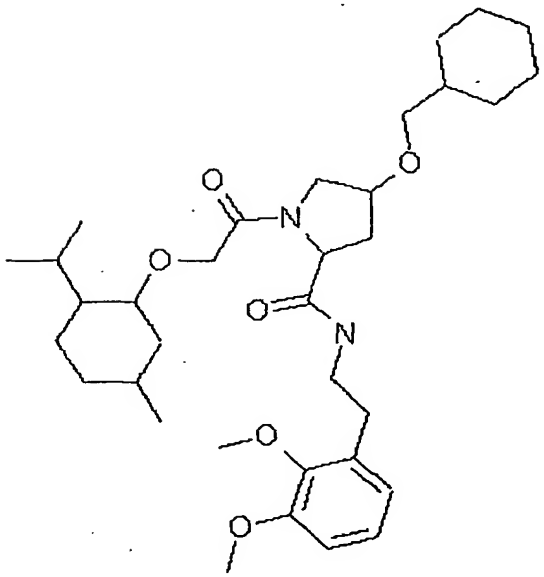


FIG. 149

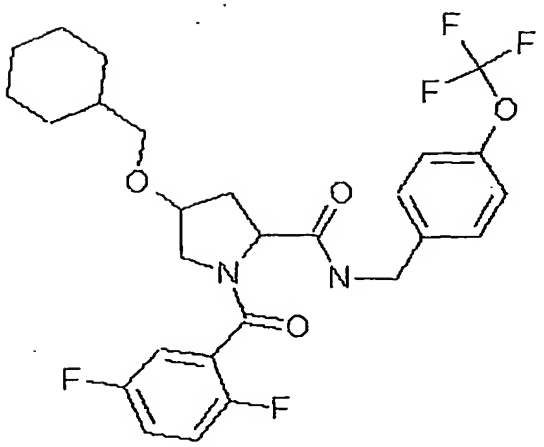


FIG. 150

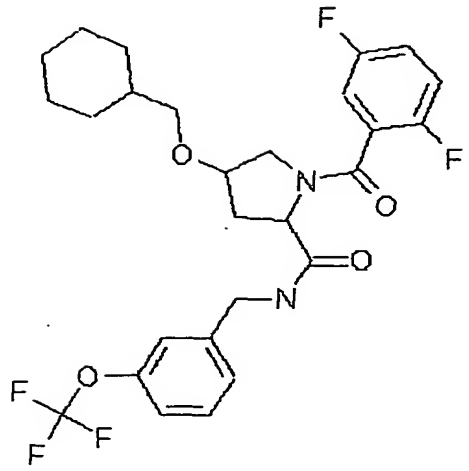


FIG. 151

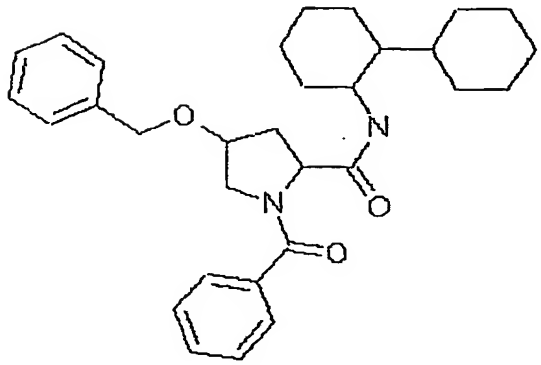


FIG. 152

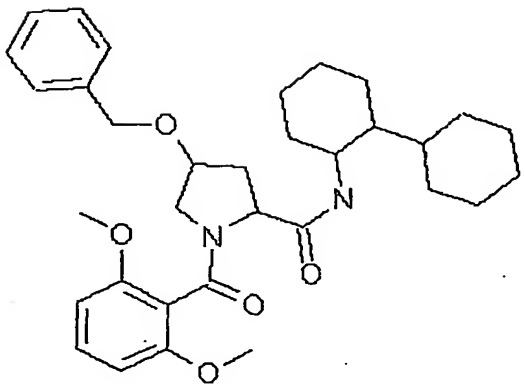


FIG. 153

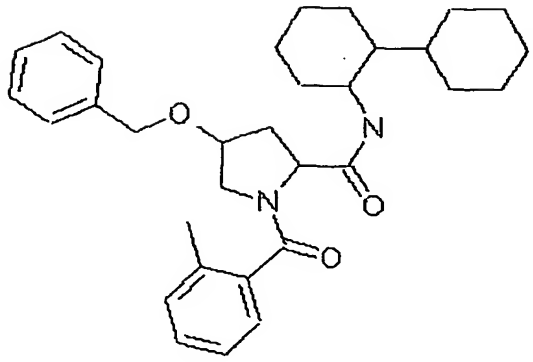


FIG. 154

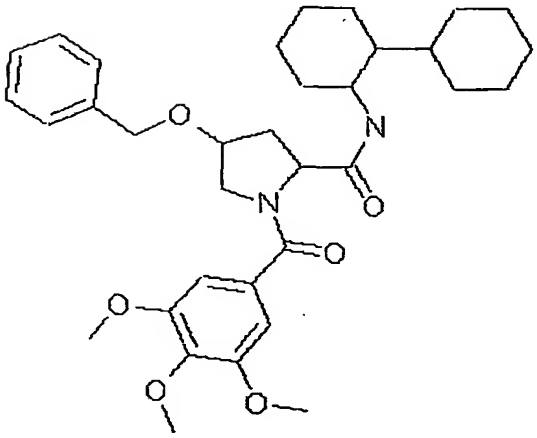


FIG. 155

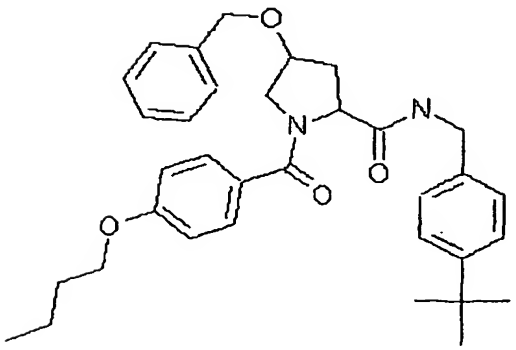


FIG. 156

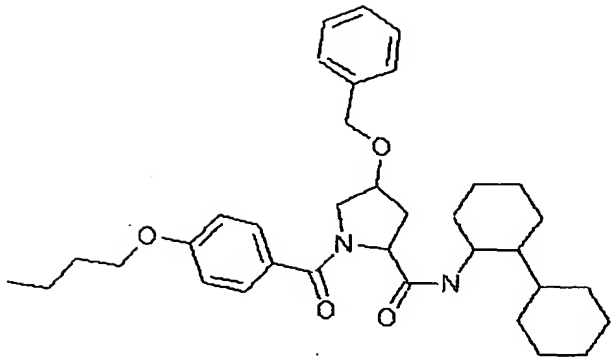


FIG. 157

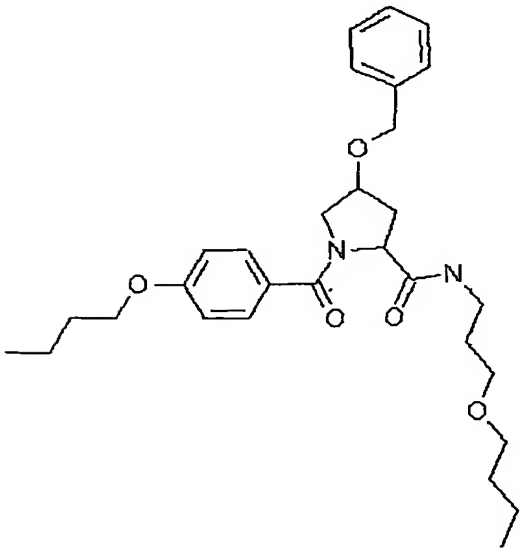


FIG. 158

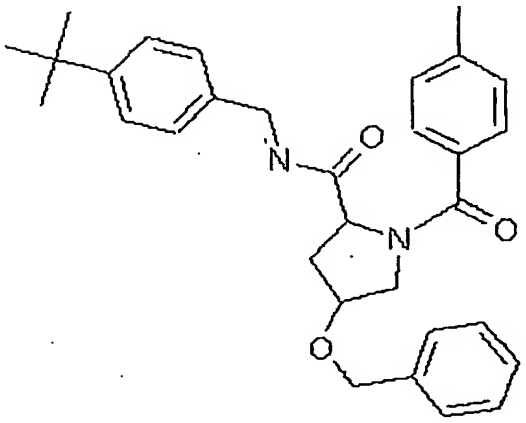


FIG. 159

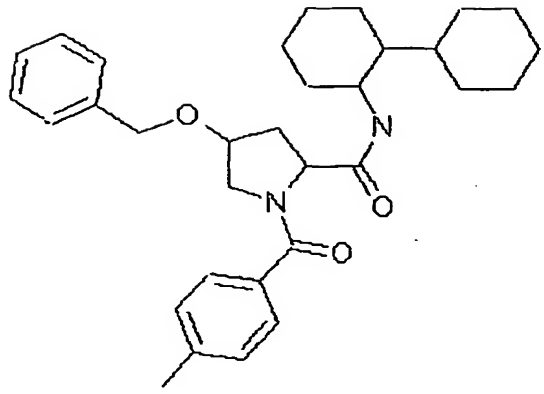


FIG. 160

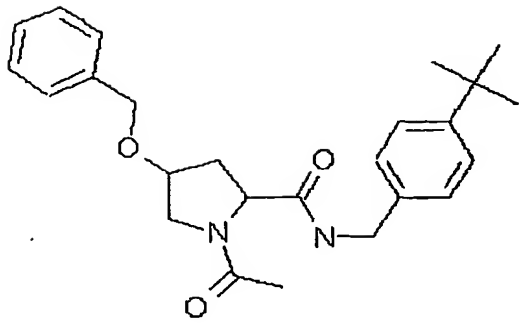


FIG. 161

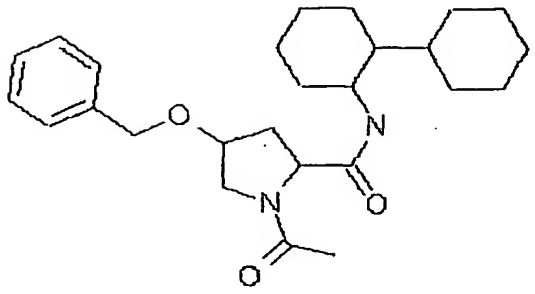


FIG. 162

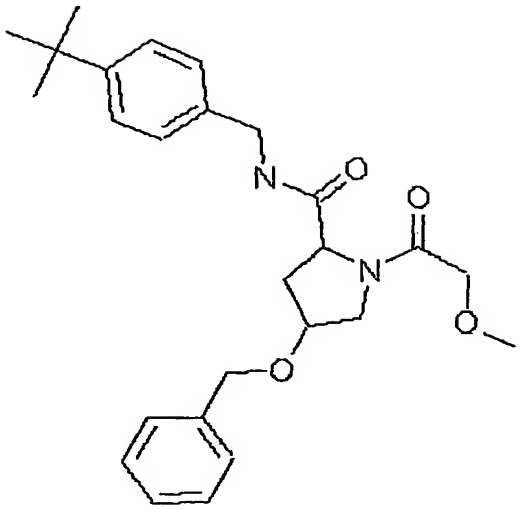


FIG. 163

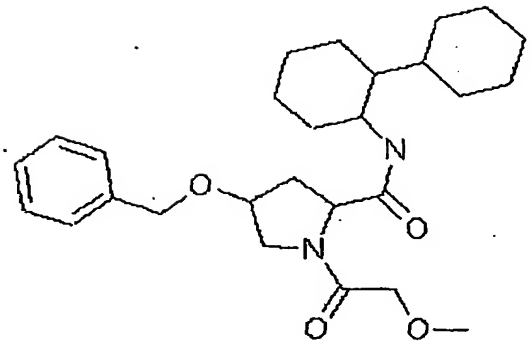


FIG. 164

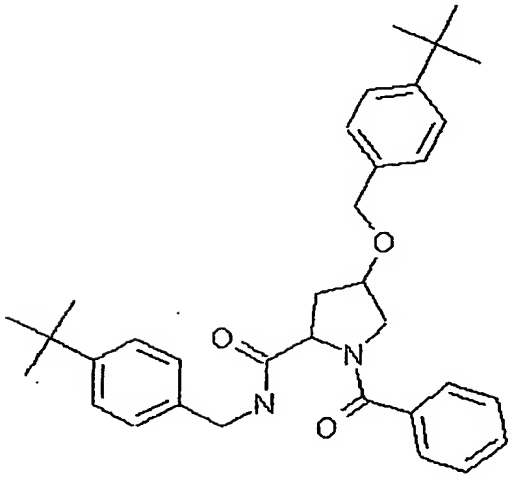


FIG. 165

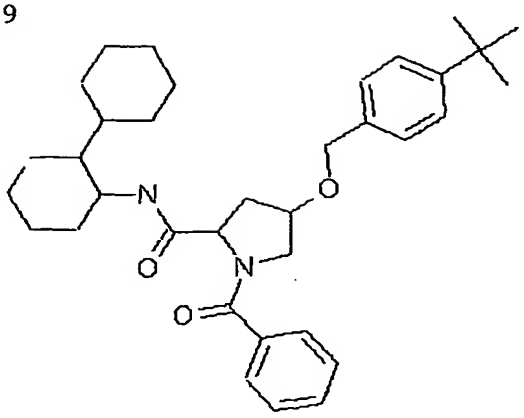


FIG. 166

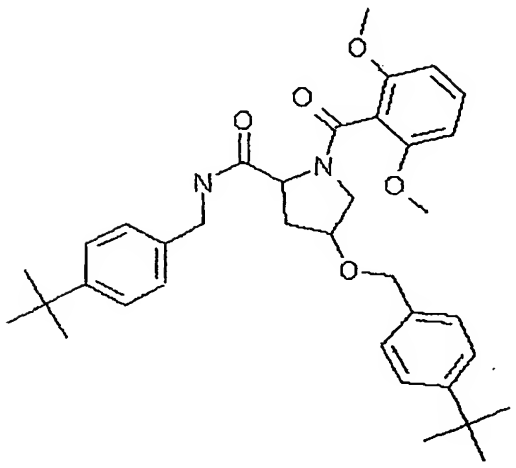


FIG. 167

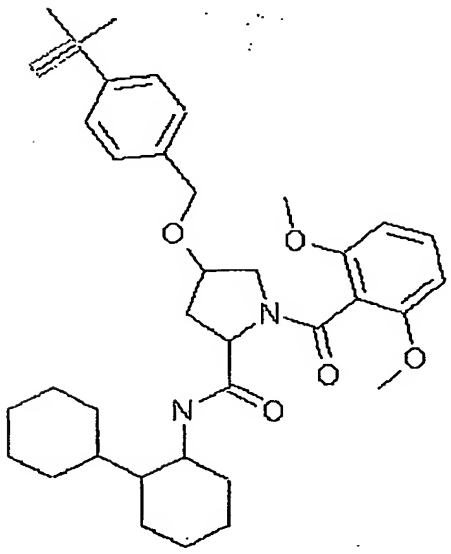


FIG. 168

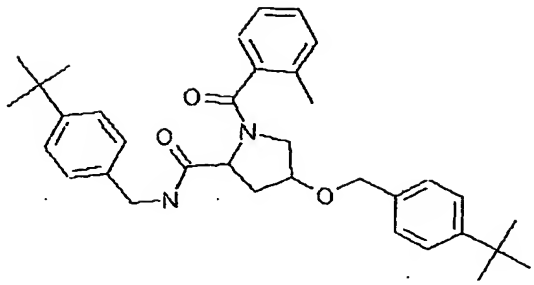


FIG. 169

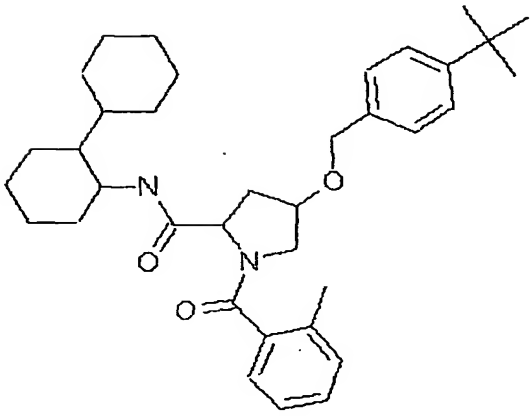


FIG. 170

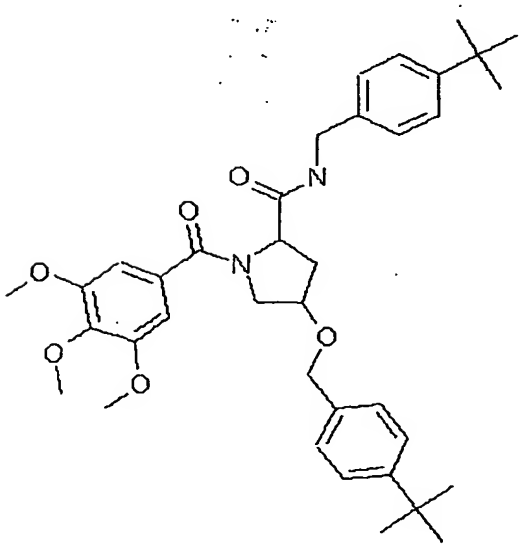


FIG. 171

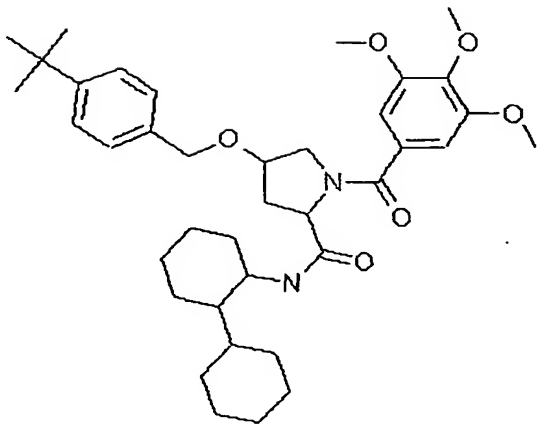


FIG. 172

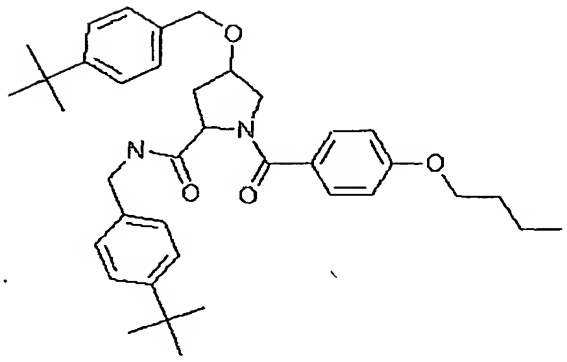


FIG. 173

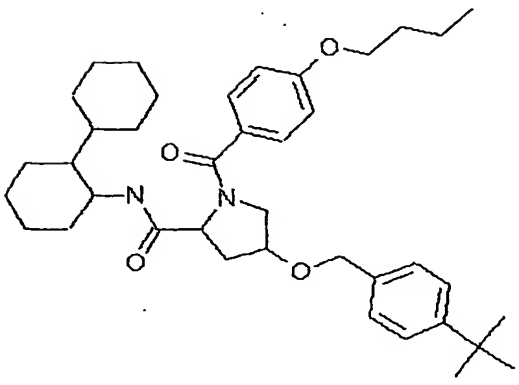


FIG. 174

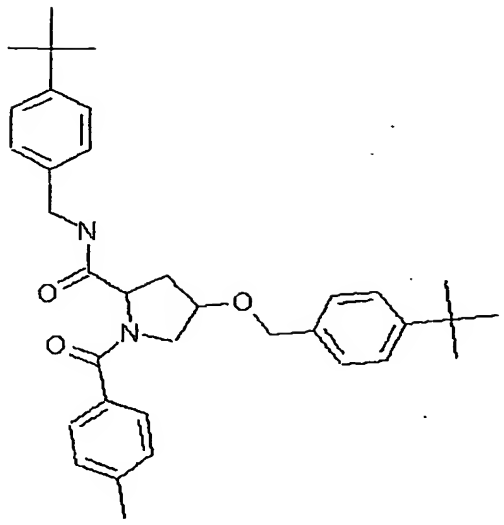


FIG. 175

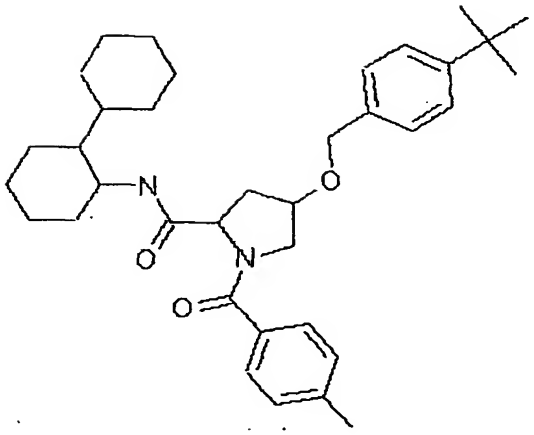


FIG. 176

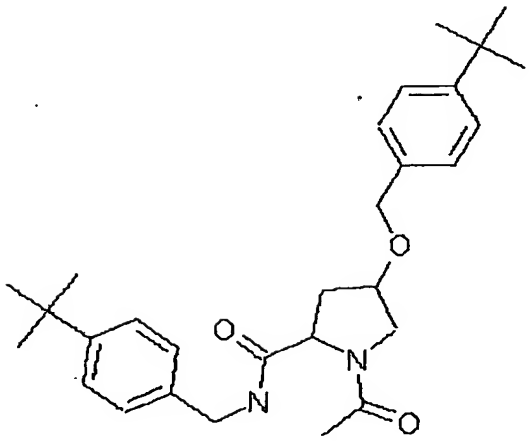


FIG. 177

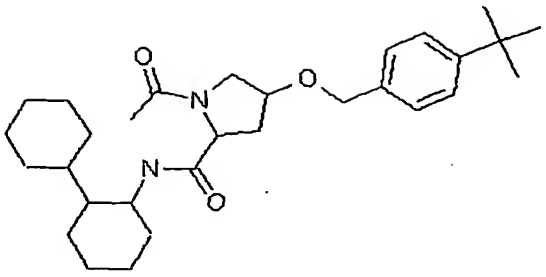


FIG. 178

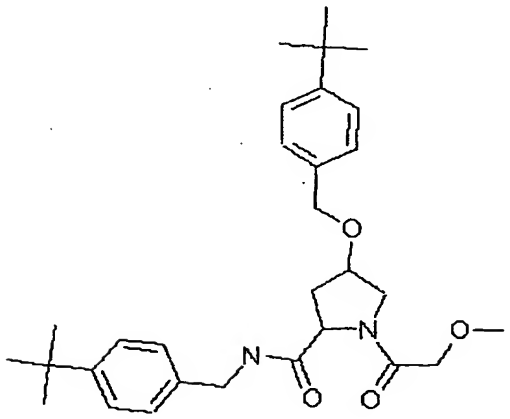


FIG. 179

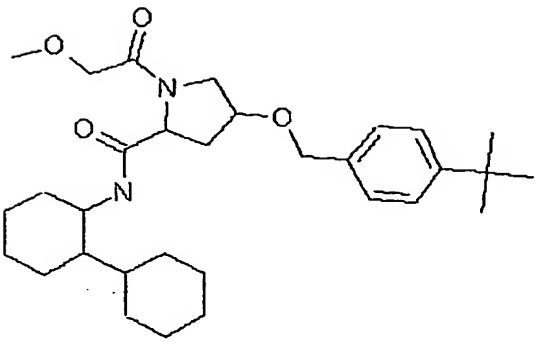


FIG. 180

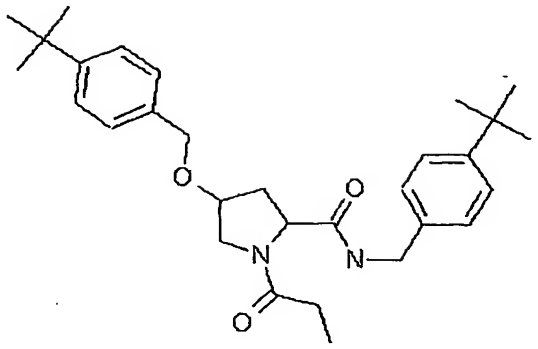


FIG. 181

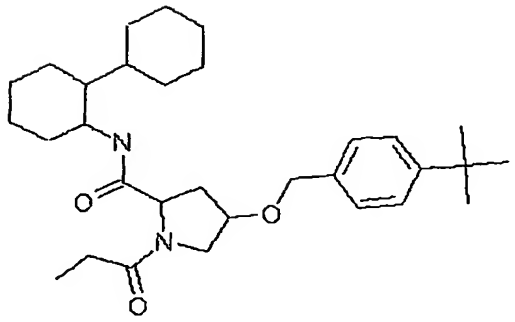


FIG. 182

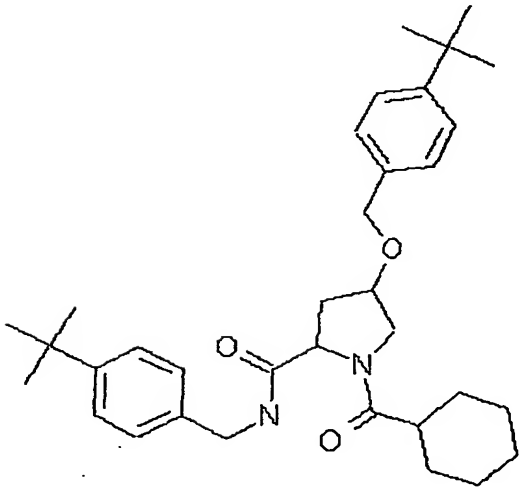


FIG. 183

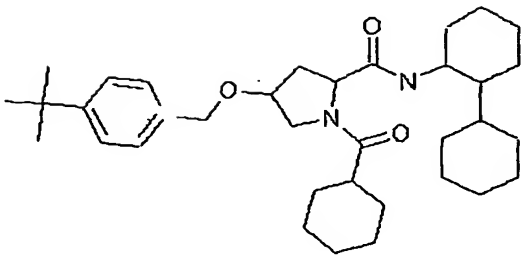


FIG. 184

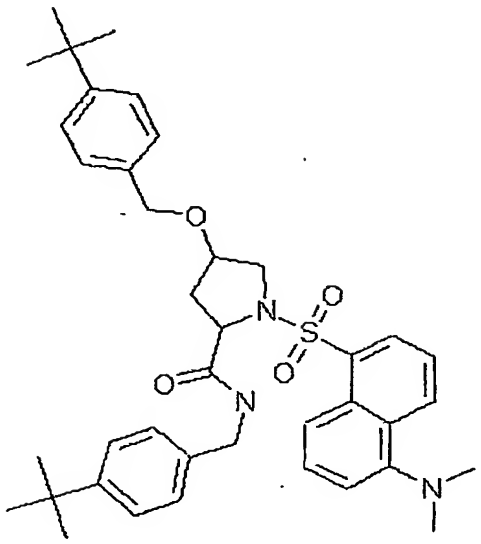


FIG. 185

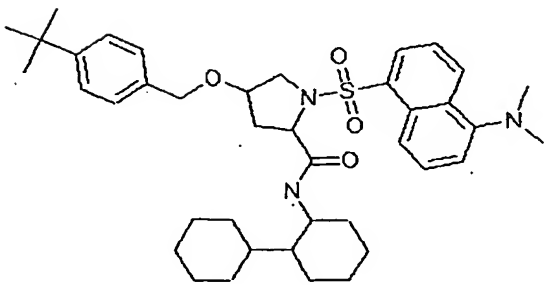


FIG. 186

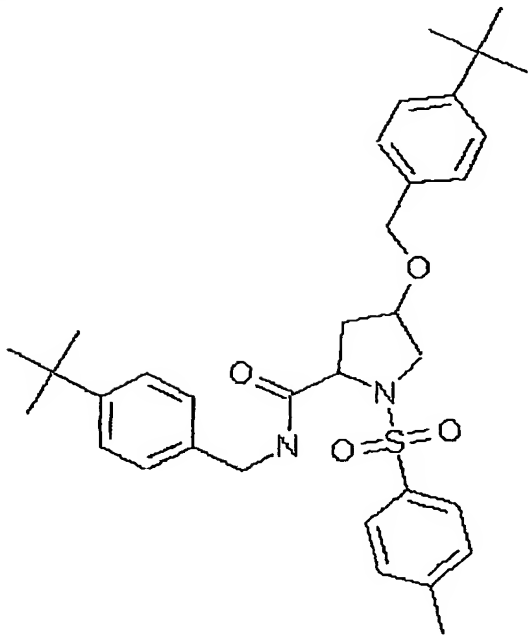


FIG. 187

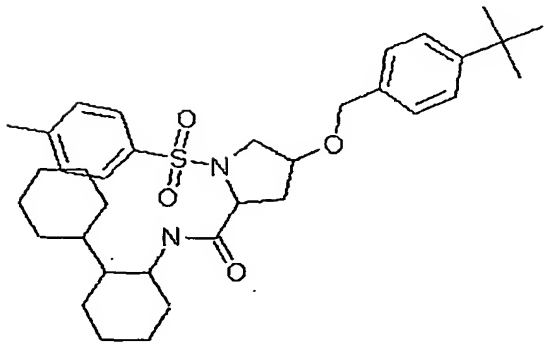


FIG. 188

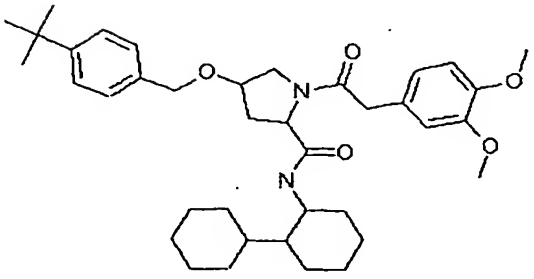


FIG. 189

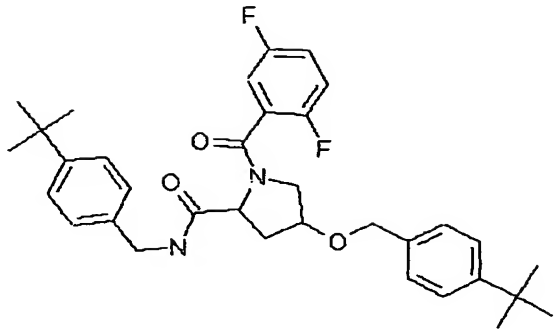


FIG. 190

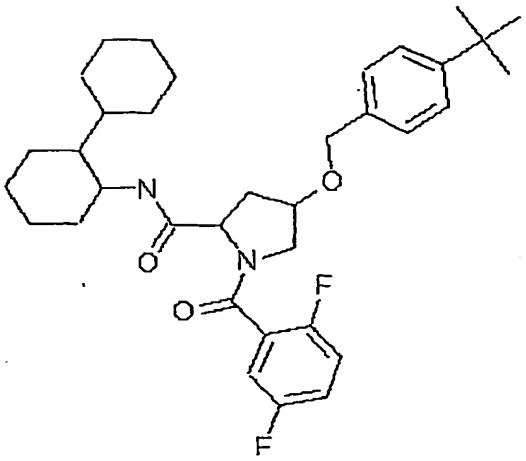


FIG. 191

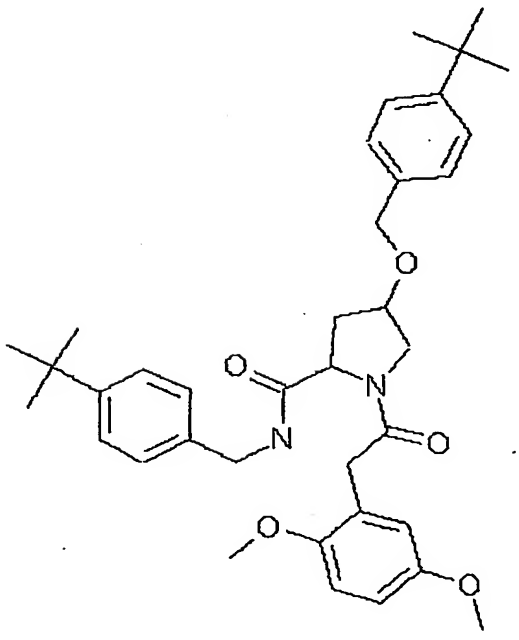


FIG. 192

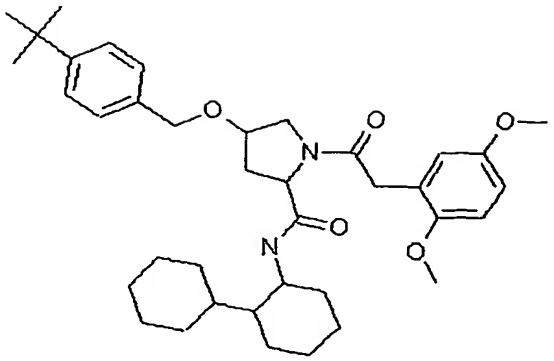


FIG. 193

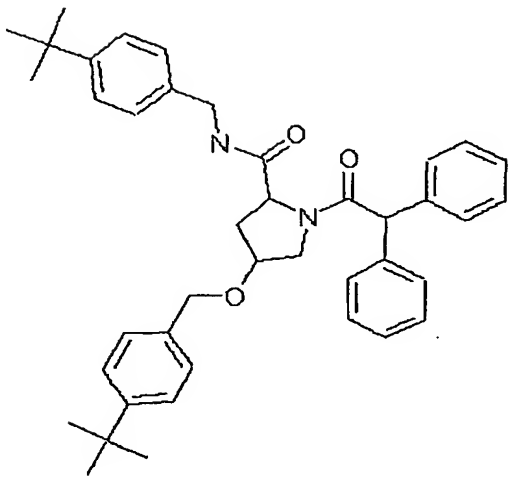


FIG. 194

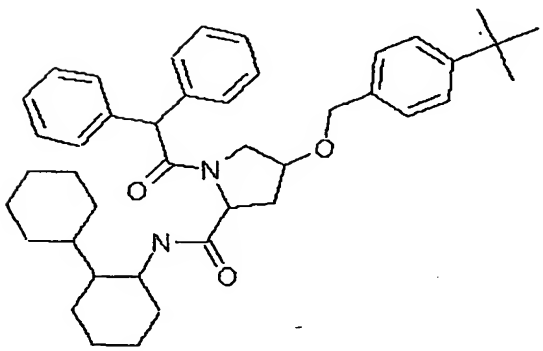


FIG. 195

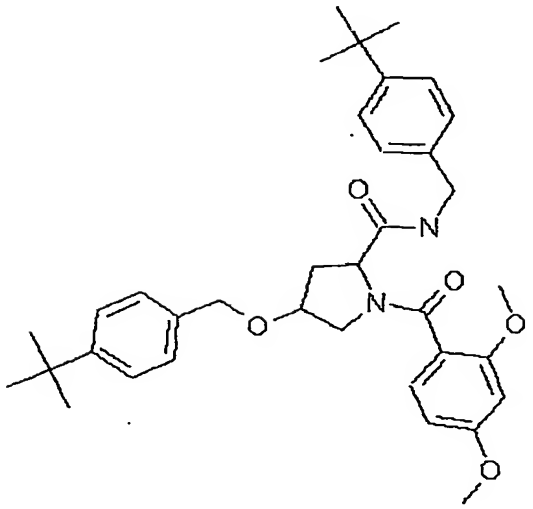


FIG. 196

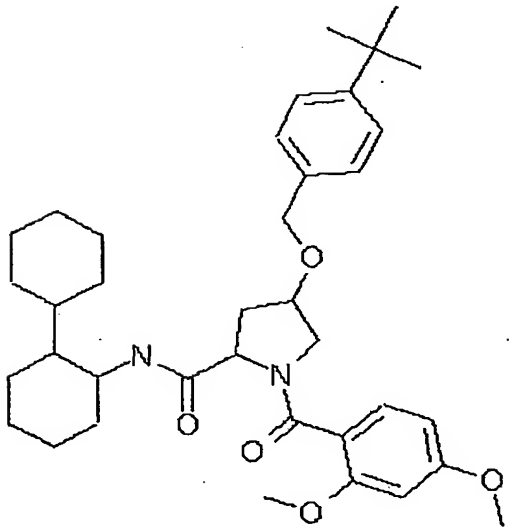


FIG. 197

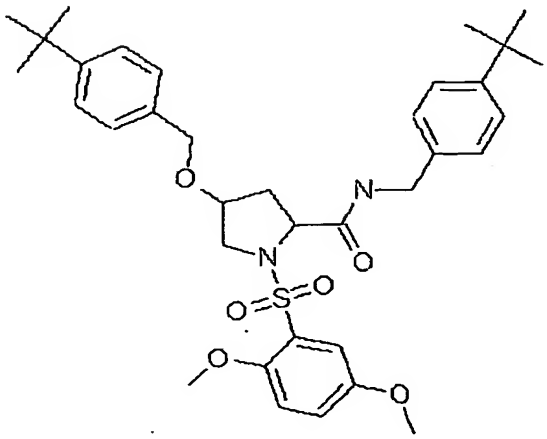


FIG. 198

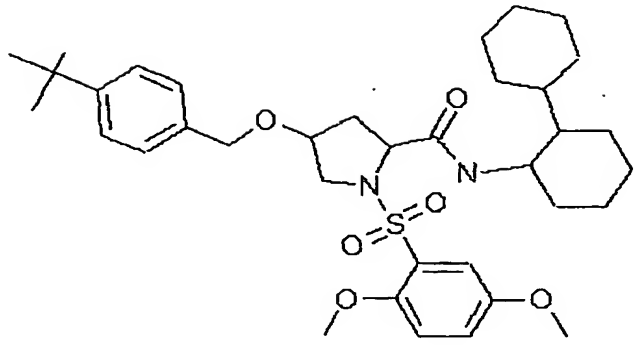


FIG. 199

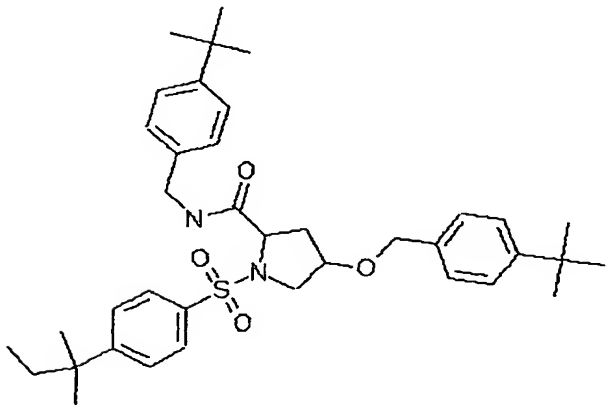


FIG. 200

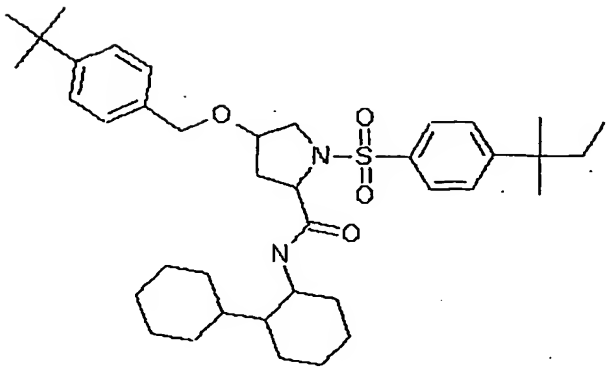


FIG. 201

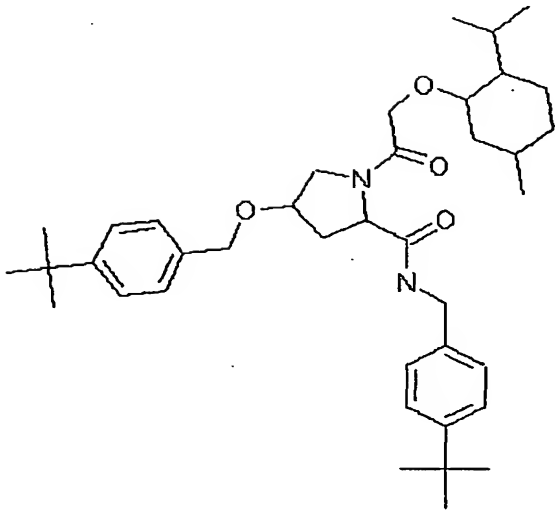


FIG. 202

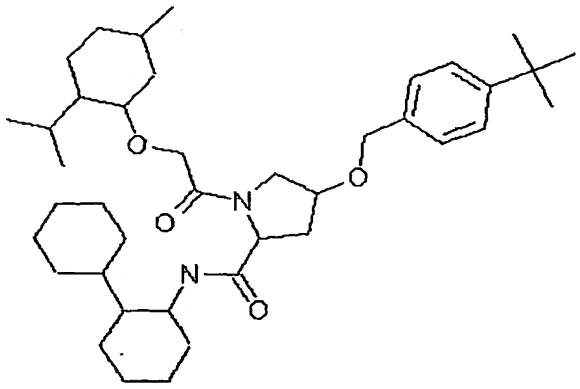


FIG. 203

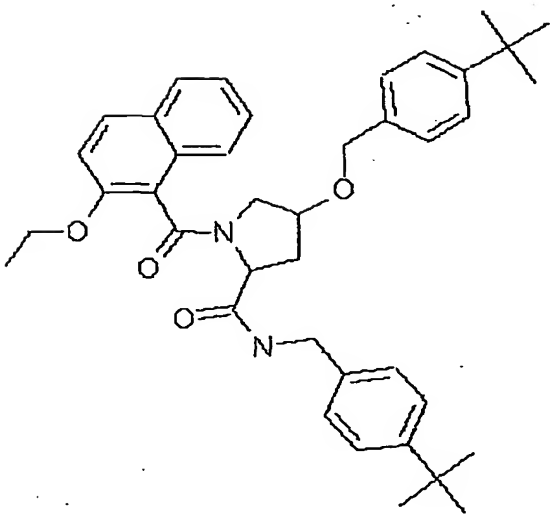


FIG. 204

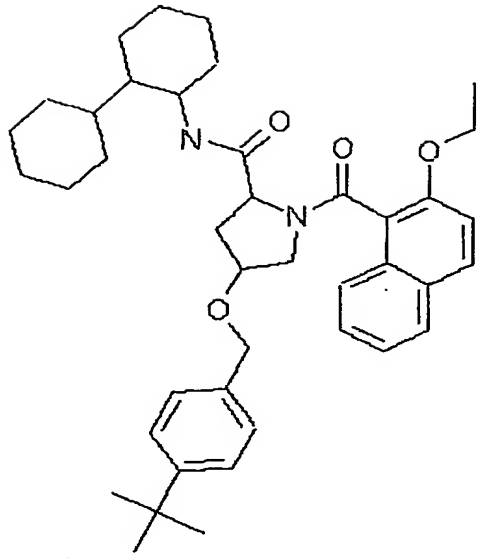


FIG. 205

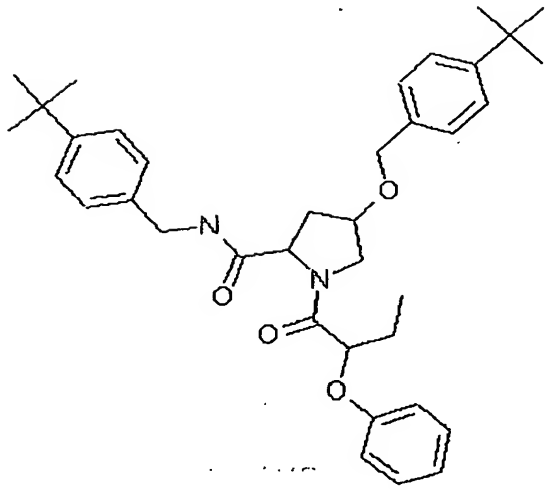


FIG. 206

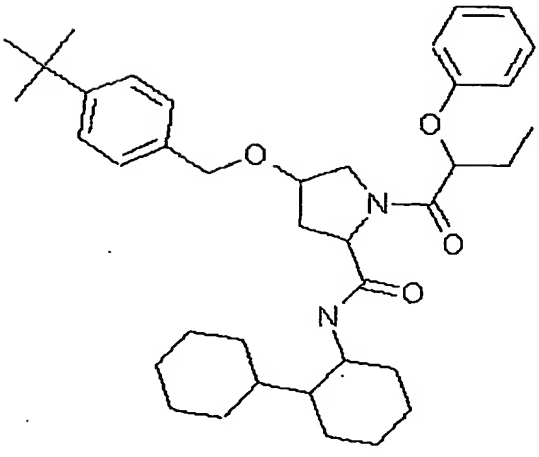


FIG. 207

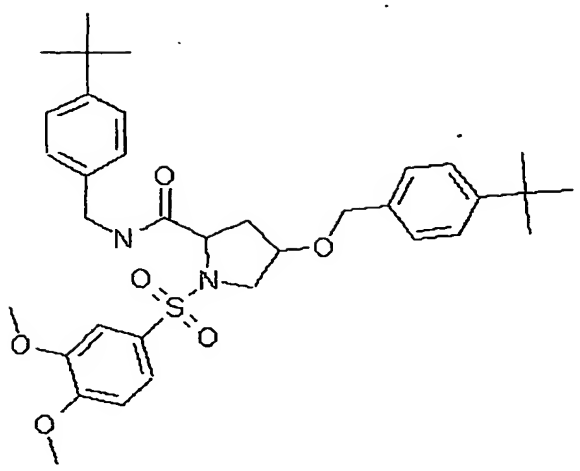


FIG. 208

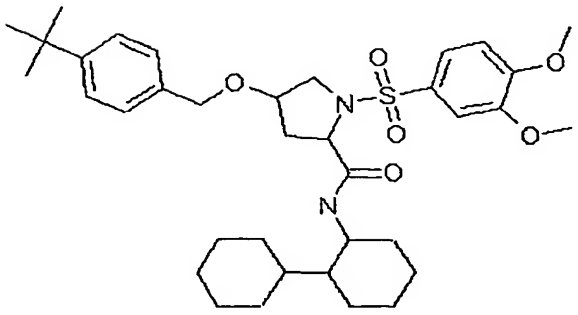


FIG. 209

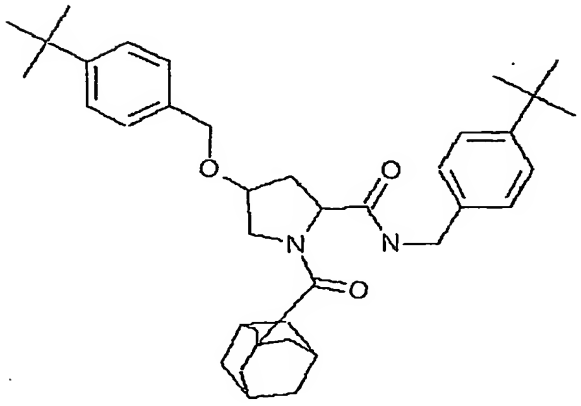


FIG. 210

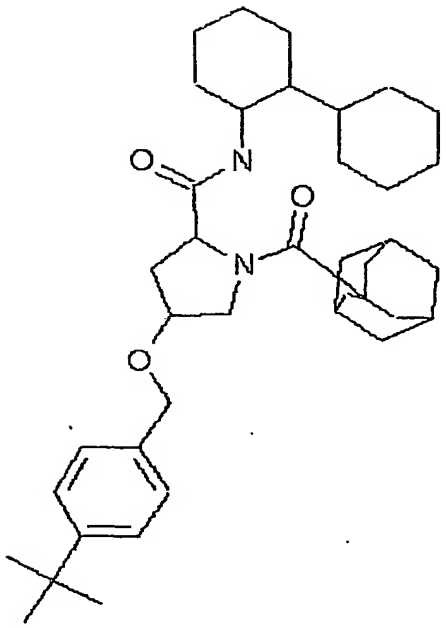


FIG. 211

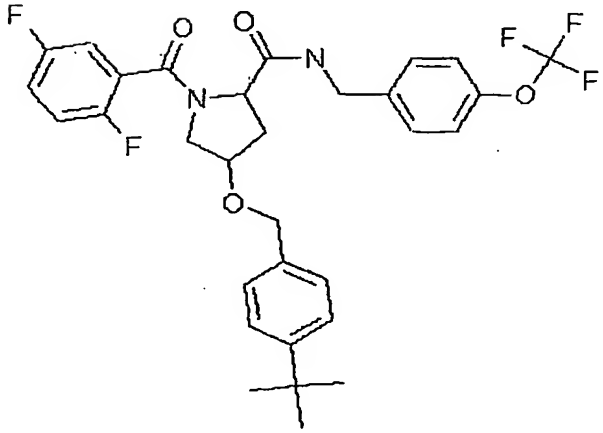


FIG. 212

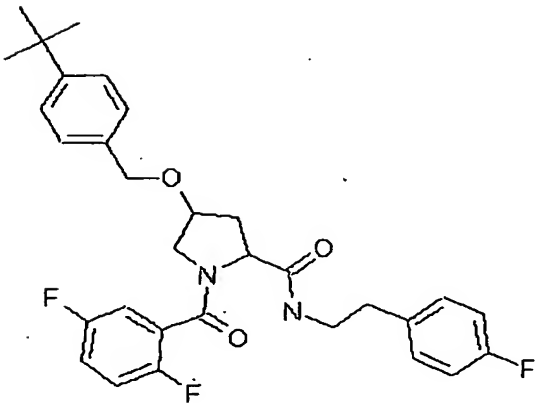


FIG. 213

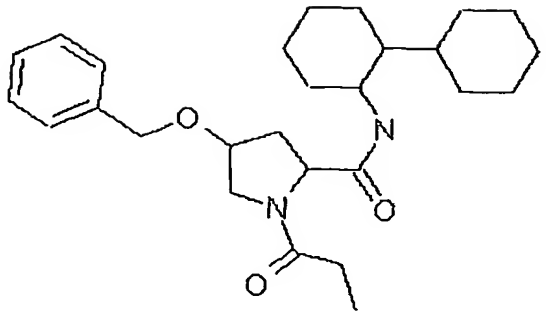


FIG. 214

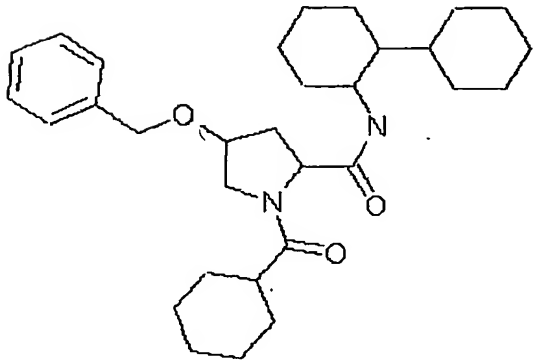


FIG. 215

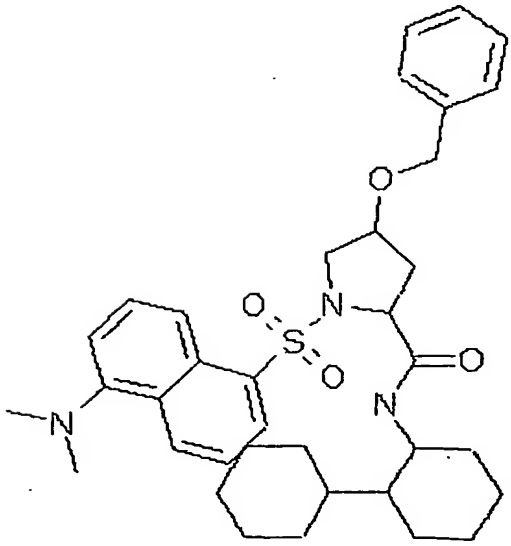


FIG. 216

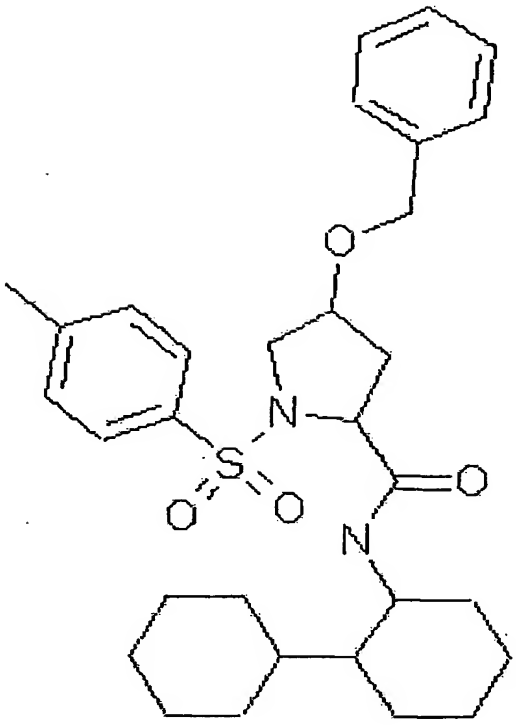


FIG. 217

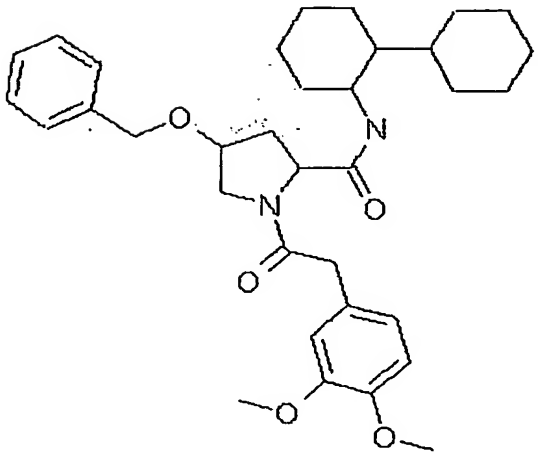


FIG. 218

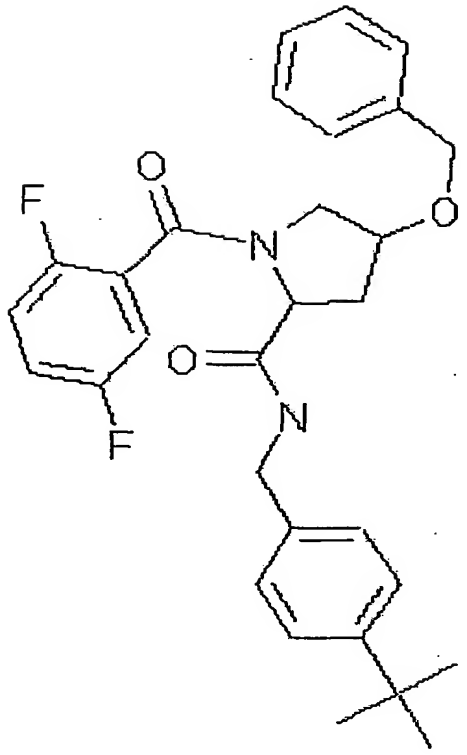


FIG. 219

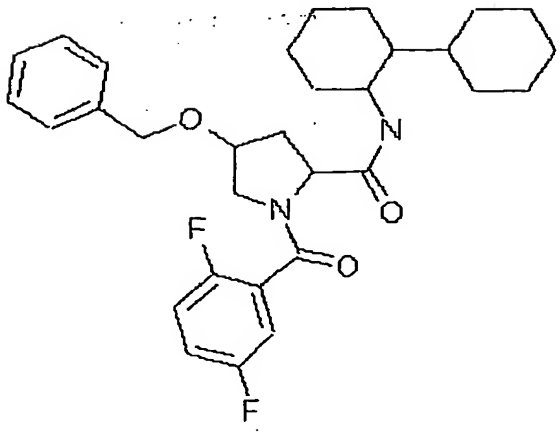


FIG. 220

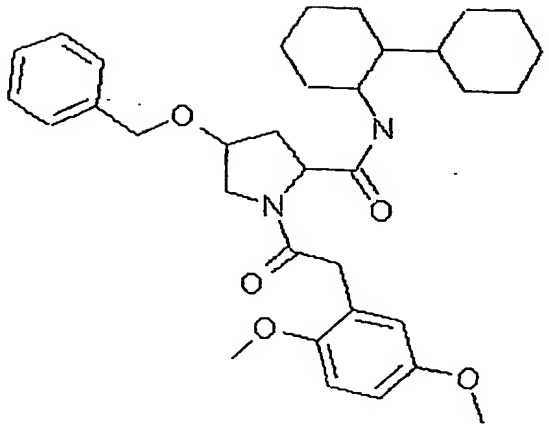


FIG. 221

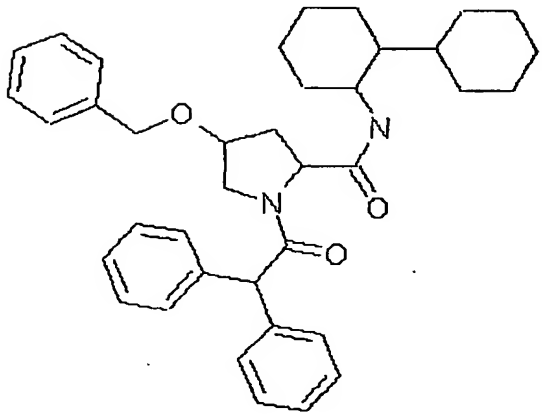


FIG. 222

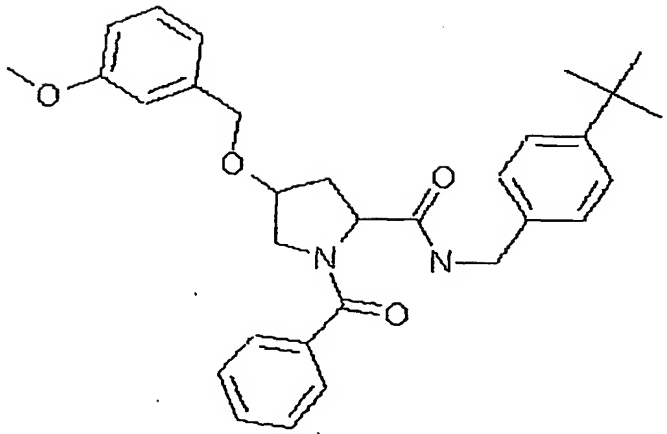


FIG. 223

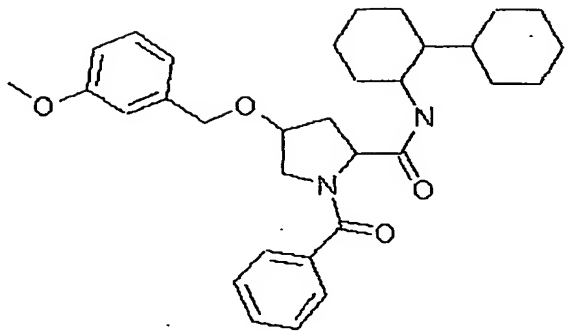


FIG. 224

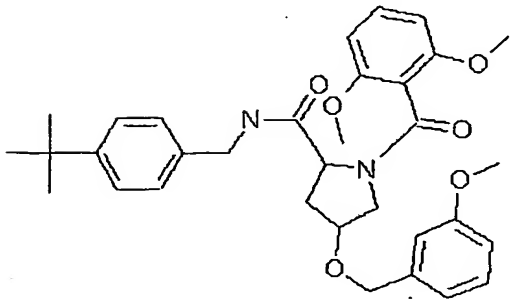


FIG. 225

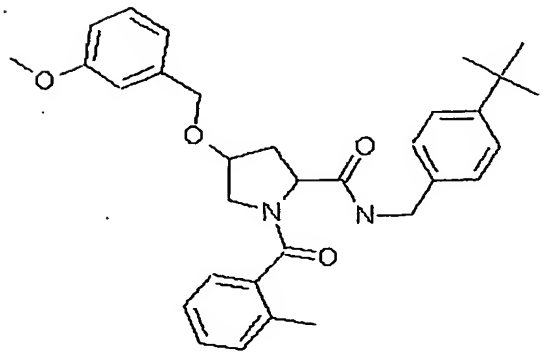


FIG. 226

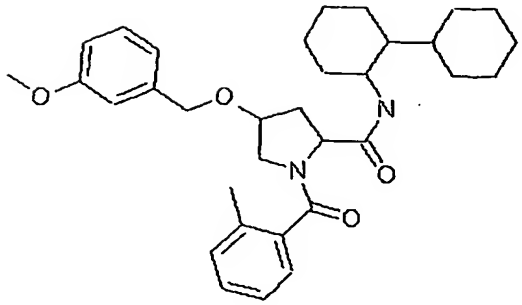


FIG. 227

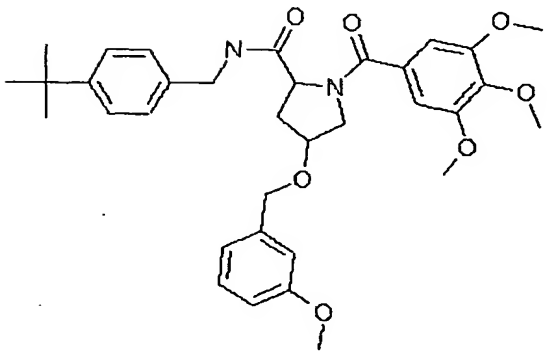


FIG. 228

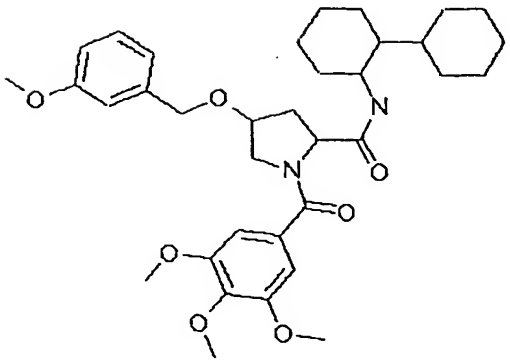


FIG. 229

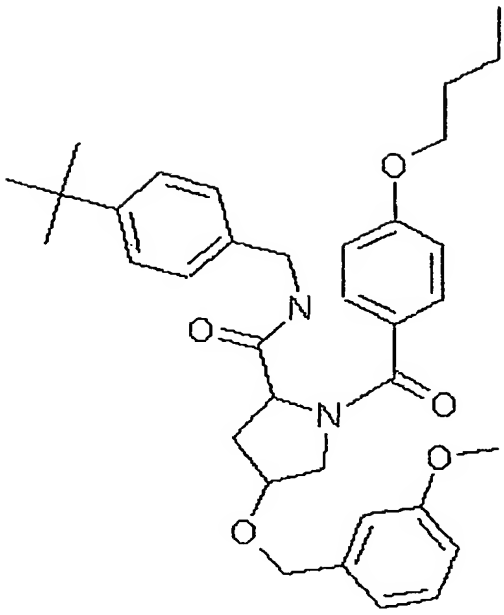


FIG. 230

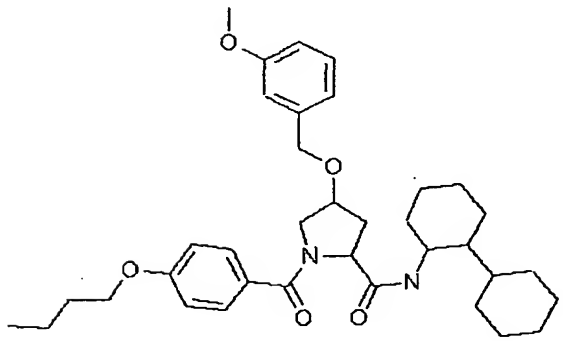


FIG. 231

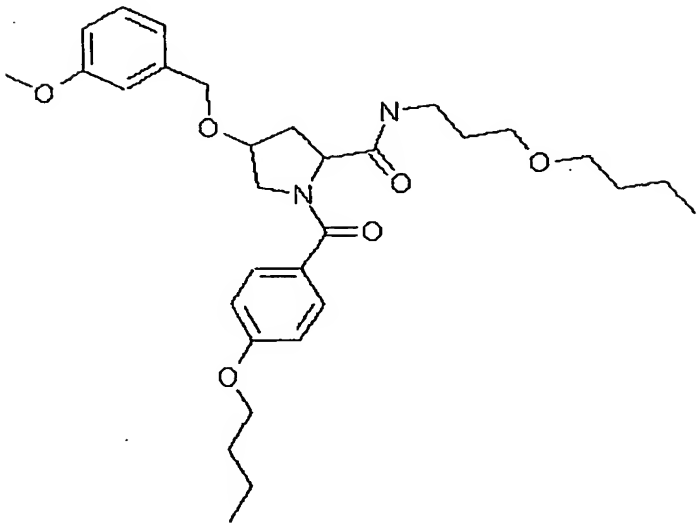


FIG. 232

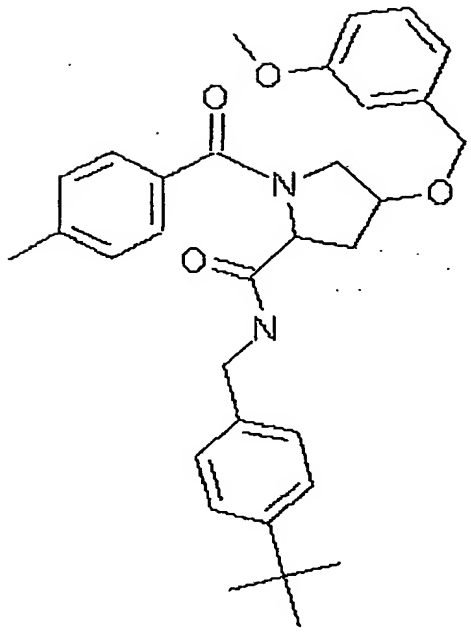


FIG. 233

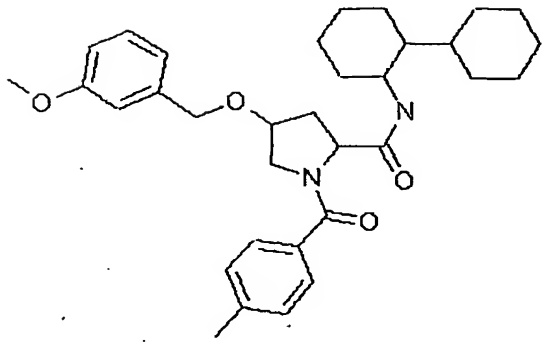


FIG. 234

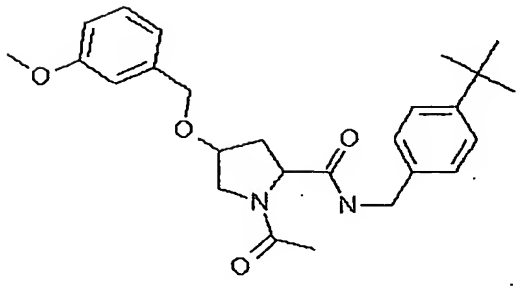


FIG. 235

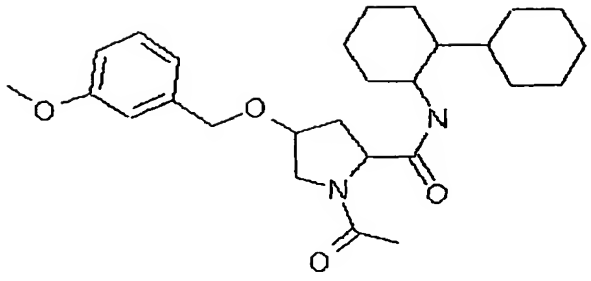


FIG. 236

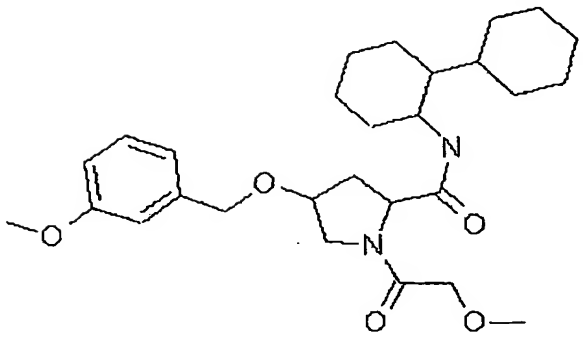


FIG. 237

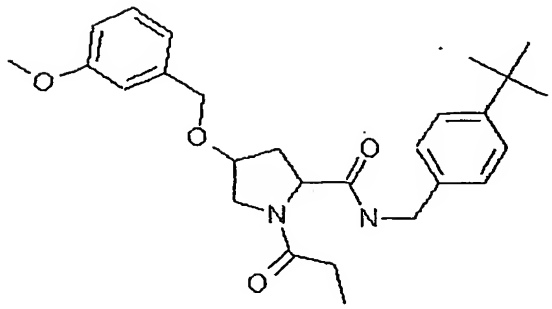


FIG. 238

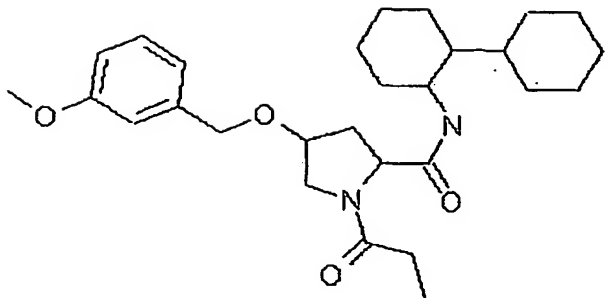


FIG. 239

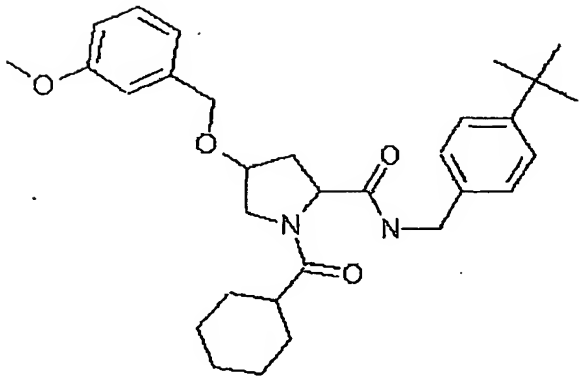


FIG. 240

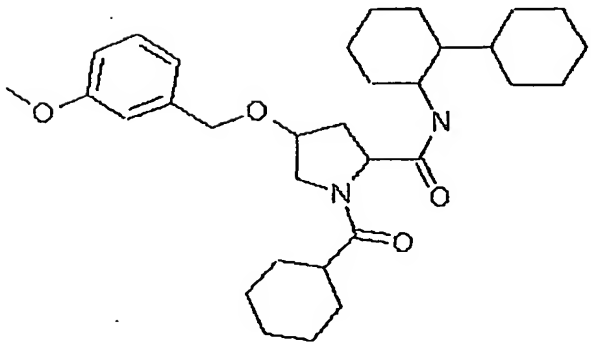


FIG. 241

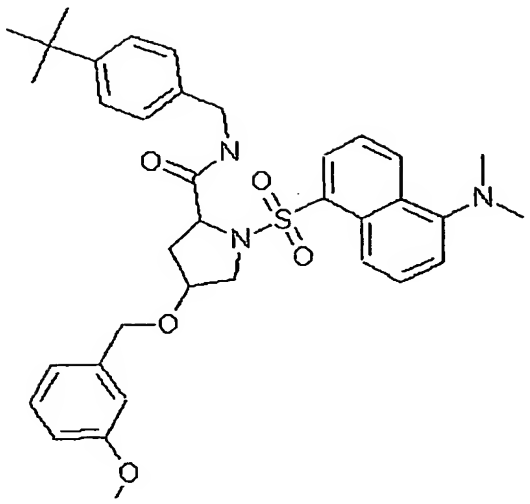


FIG. 242

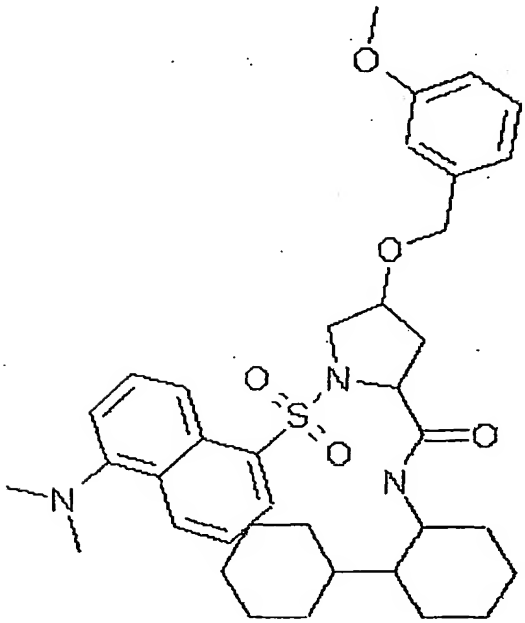


FIG. 243

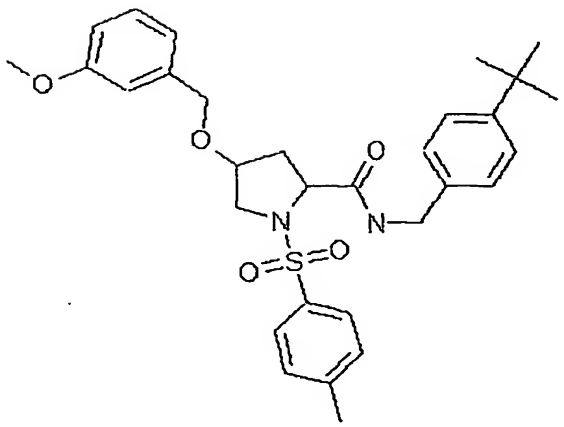


FIG. 244

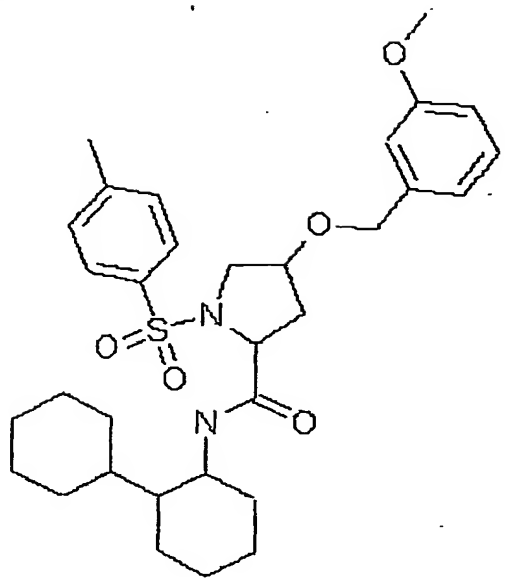


FIG. 245

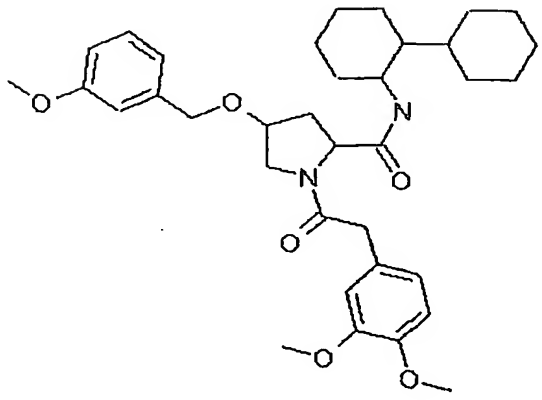


FIG. 246

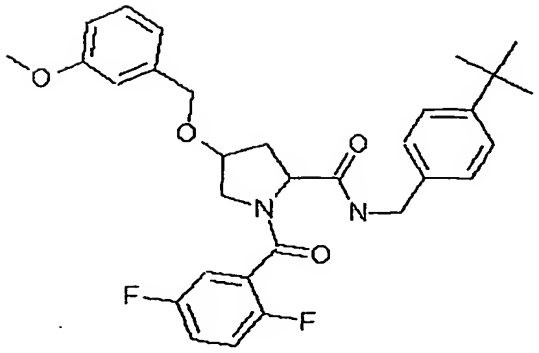


FIG. 247

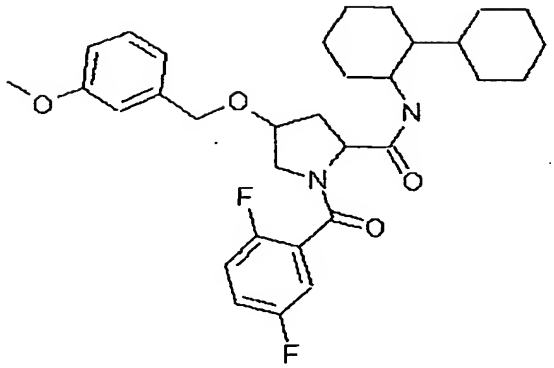


FIG. 248

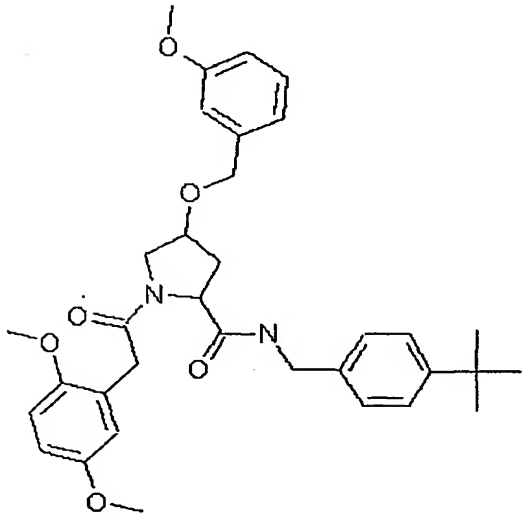


FIG. 249

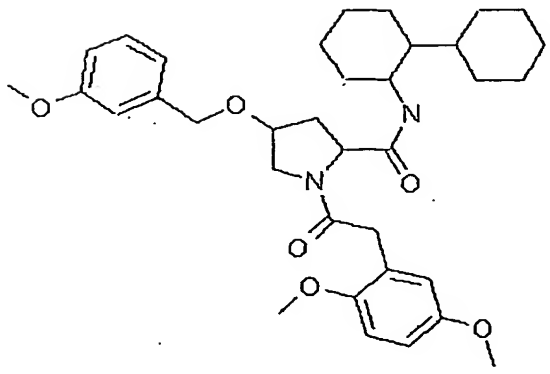


FIG. 250

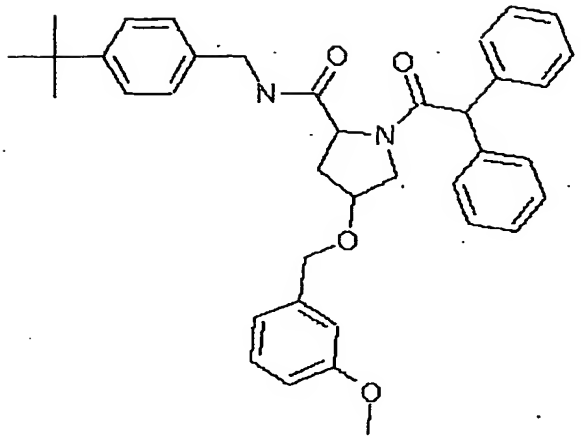


FIG. 251

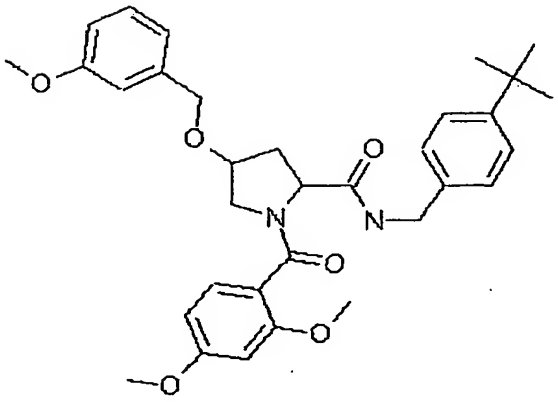


FIG. 252

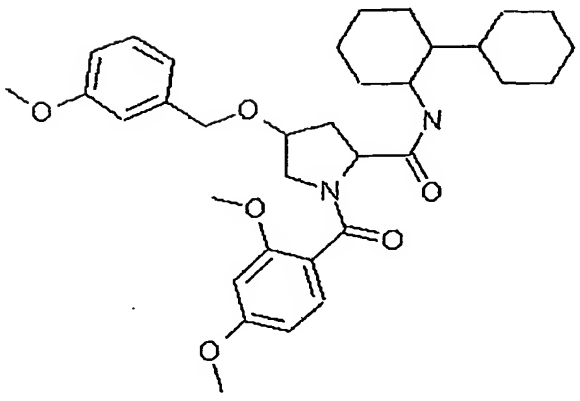


FIG. 253

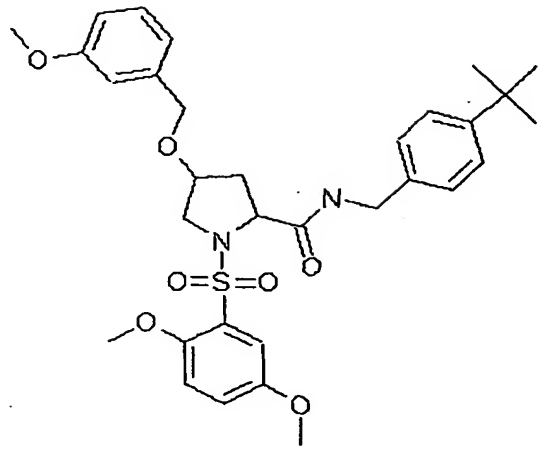


FIG. 254

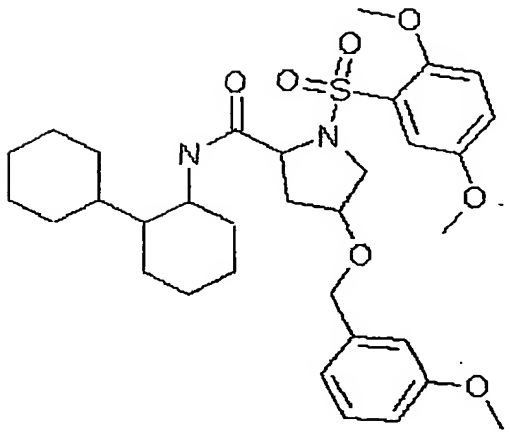


FIG. 255

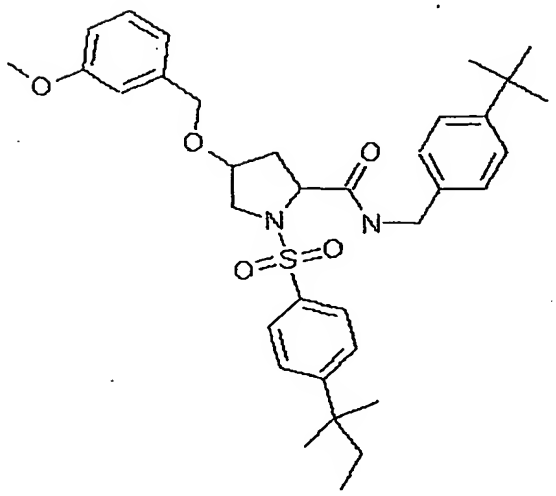


FIG. 256

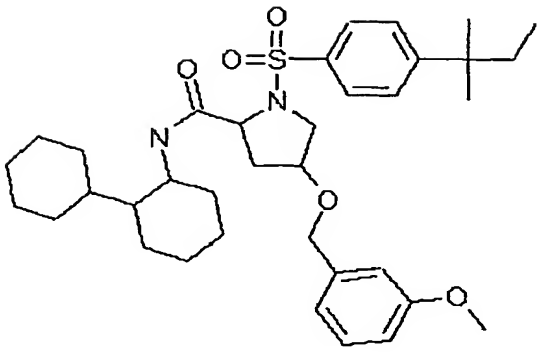


FIG. 257

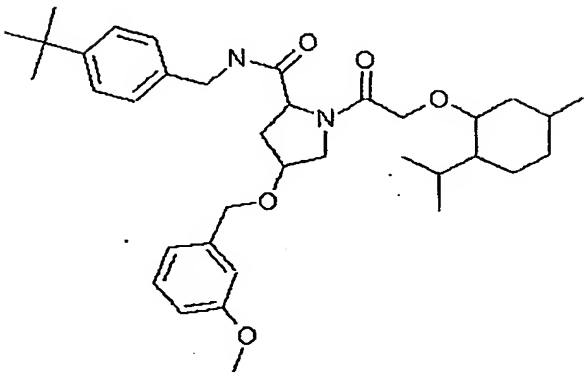


FIG. 258

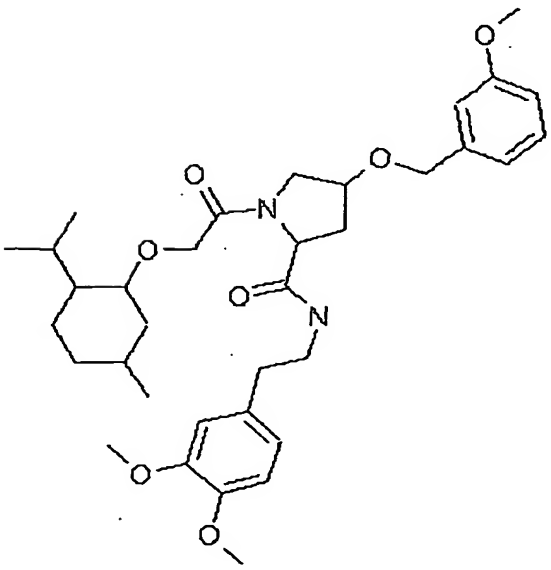


FIG. 259

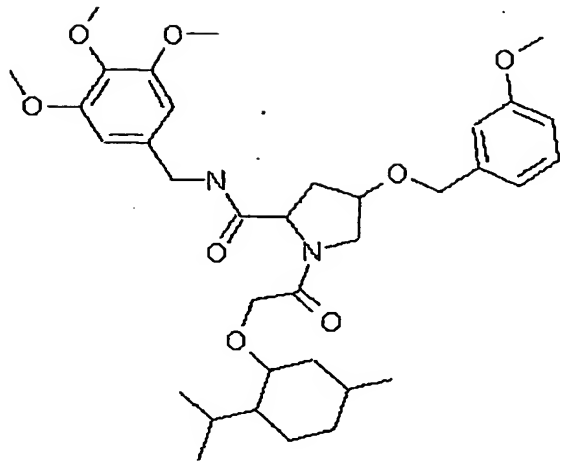


FIG. 260

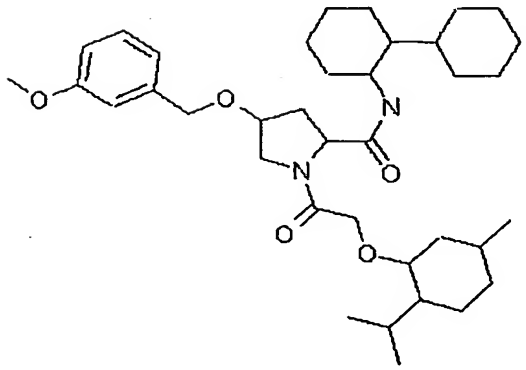


FIG. 261

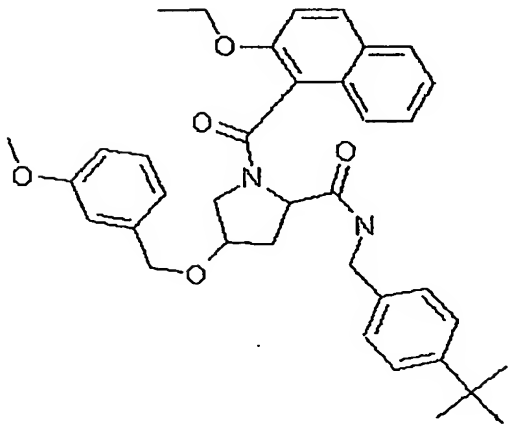


FIG. 262

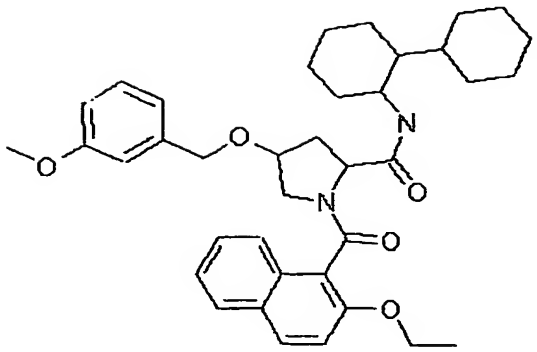


FIG. 263

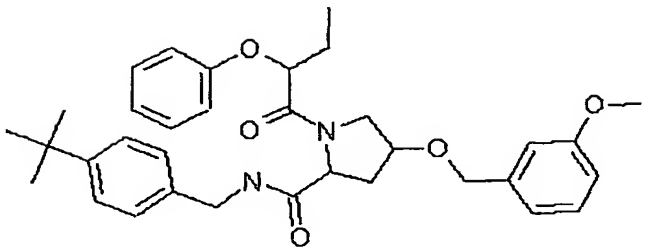


FIG. 264

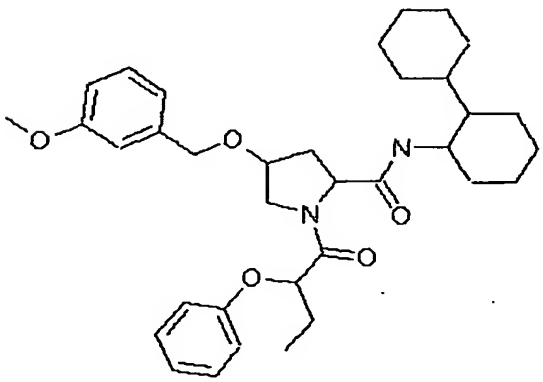


FIG. 265

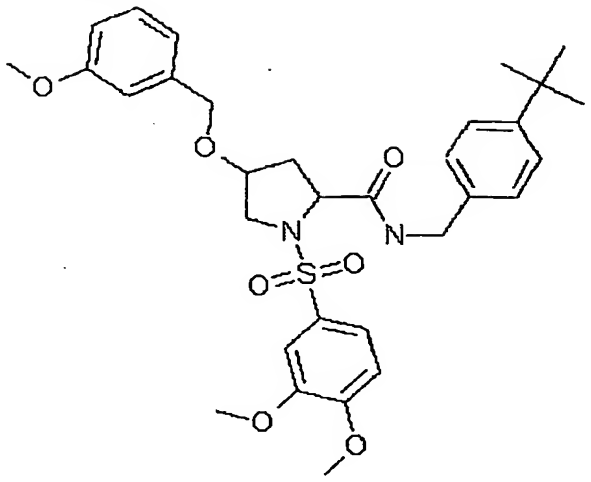


FIG. 266

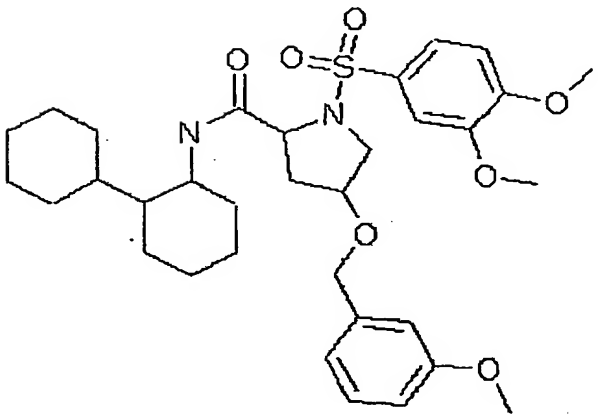


FIG. 267

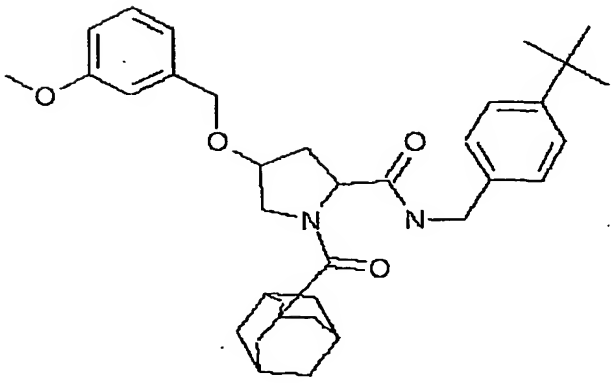


FIG. 268

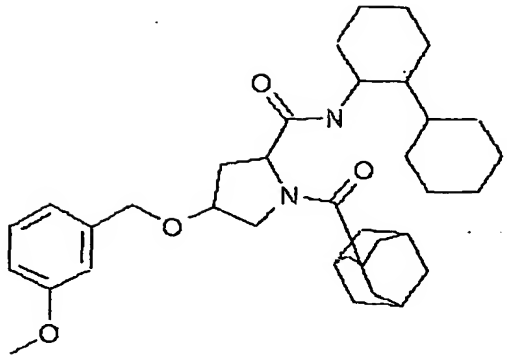


FIG. 269

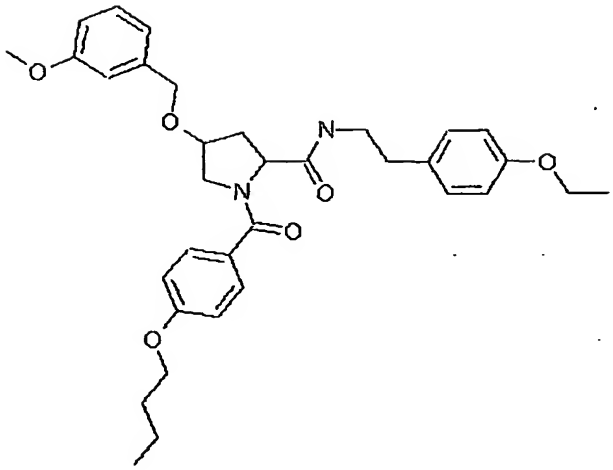


FIG. 270

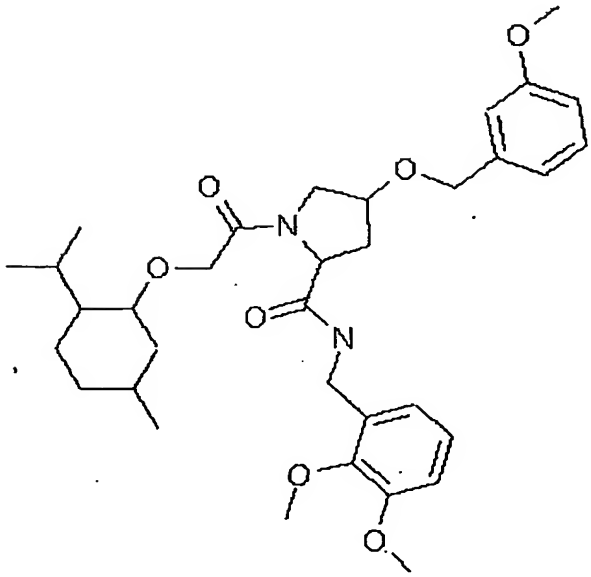


FIG. 271

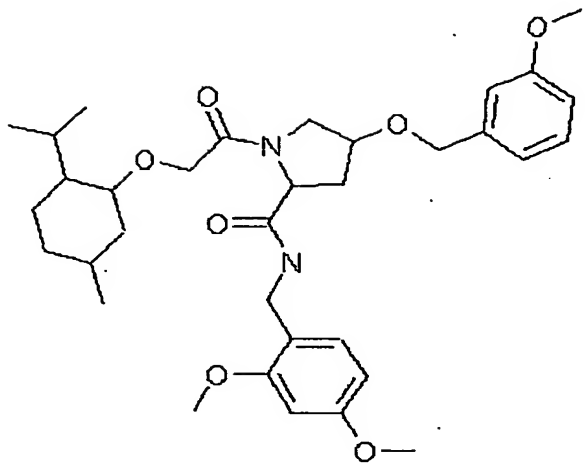


FIG. 272

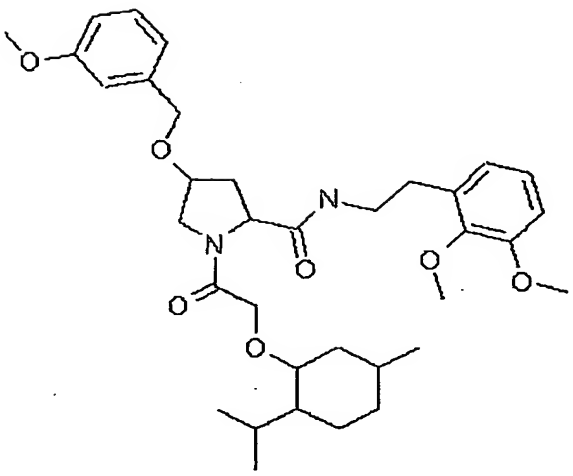


FIG. 273

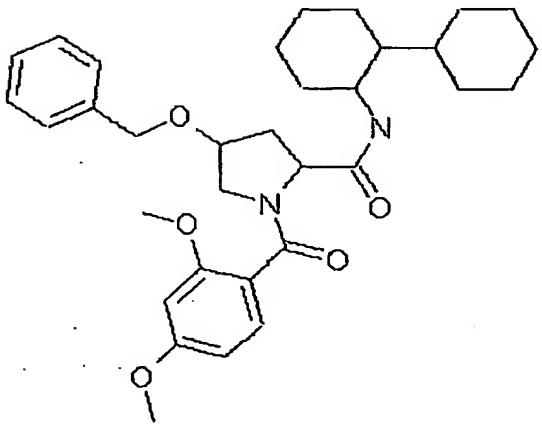


FIG. 274

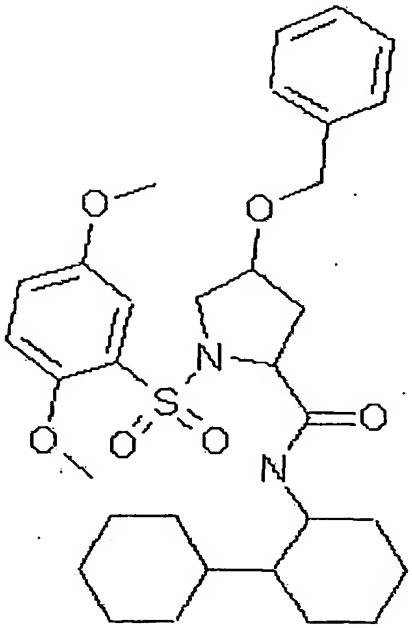


FIG. 275

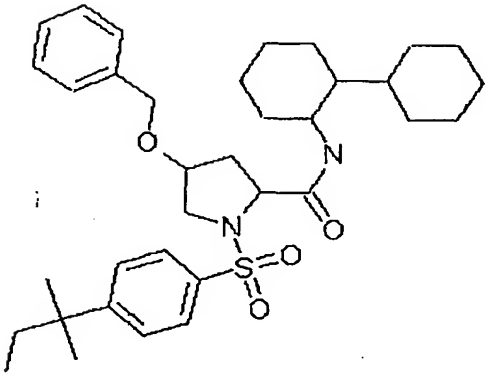


FIG. 276

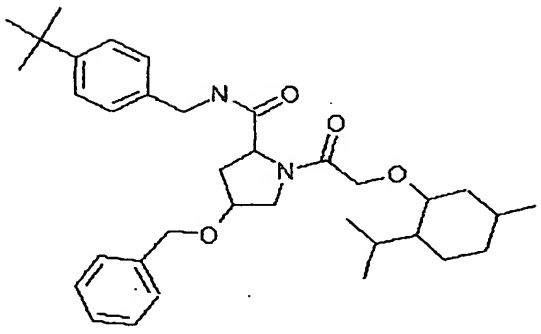


FIG. 277

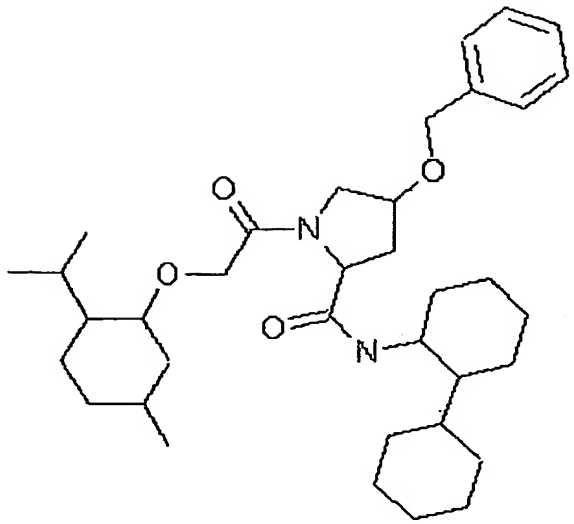


FIG. 278

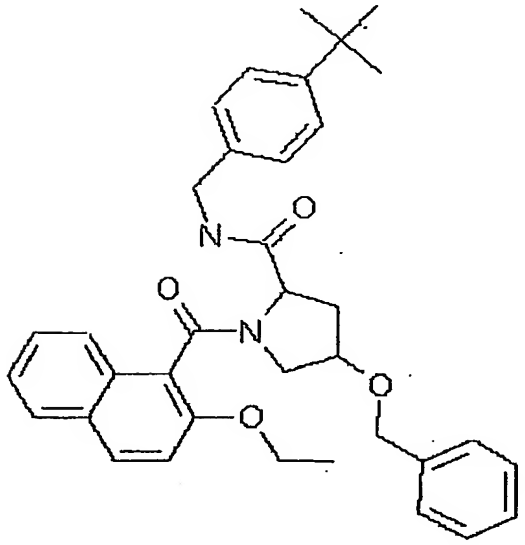


FIG. 279

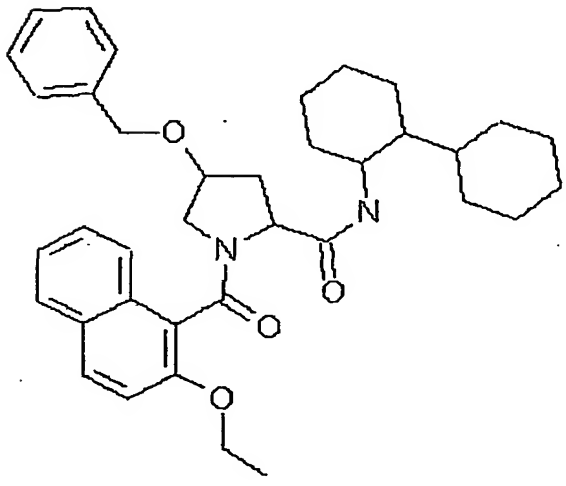


FIG. 280

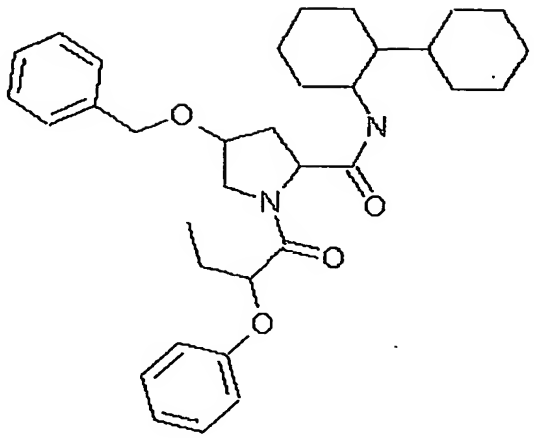


FIG. 281

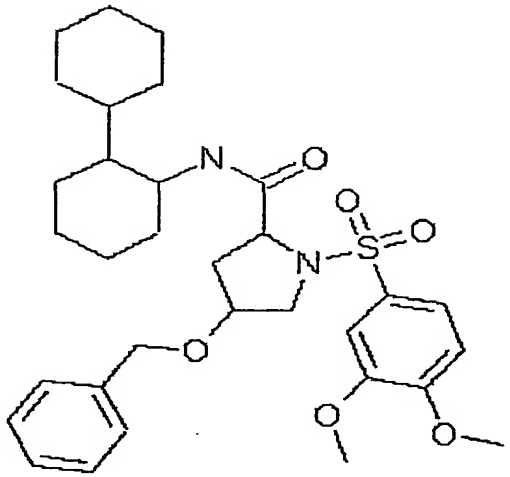


FIG. 282

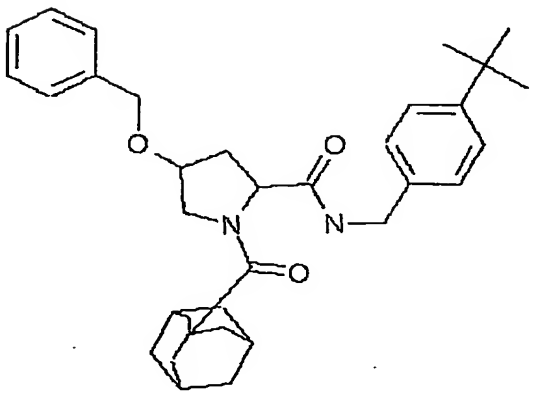


FIG. 283

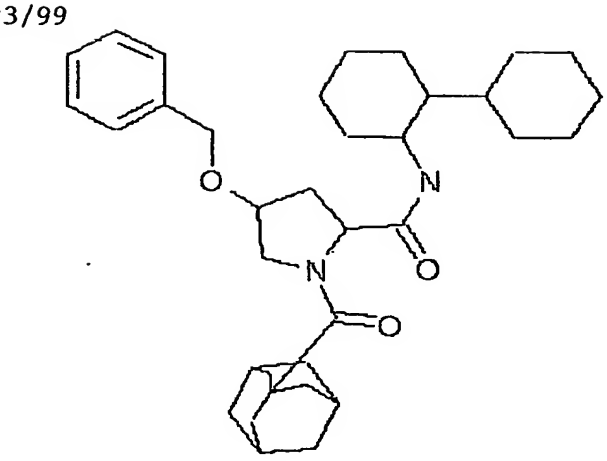


FIG. 284

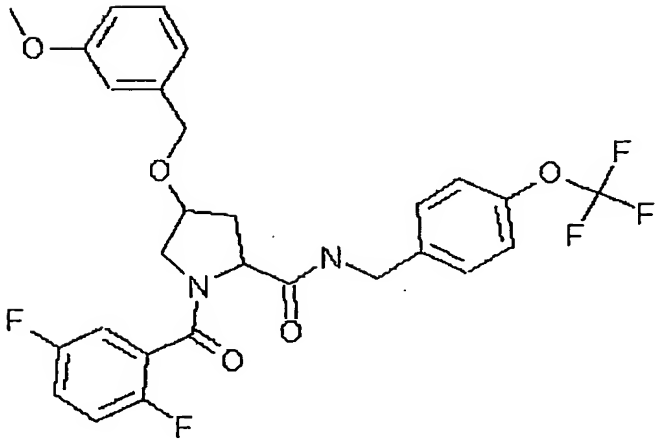


FIG. 285

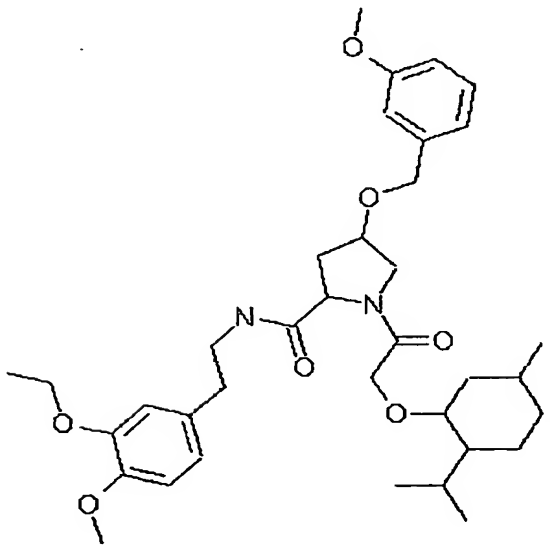


FIG. 286

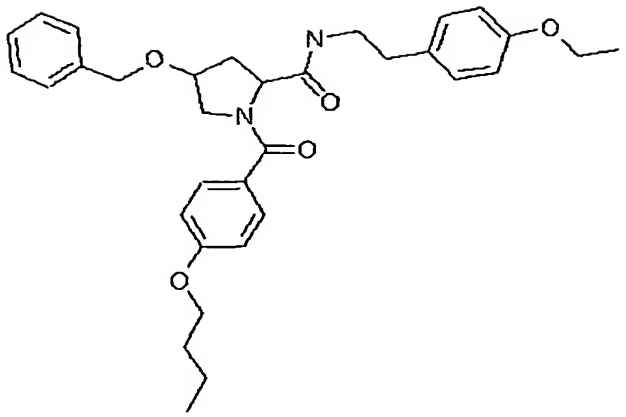


FIG. 287

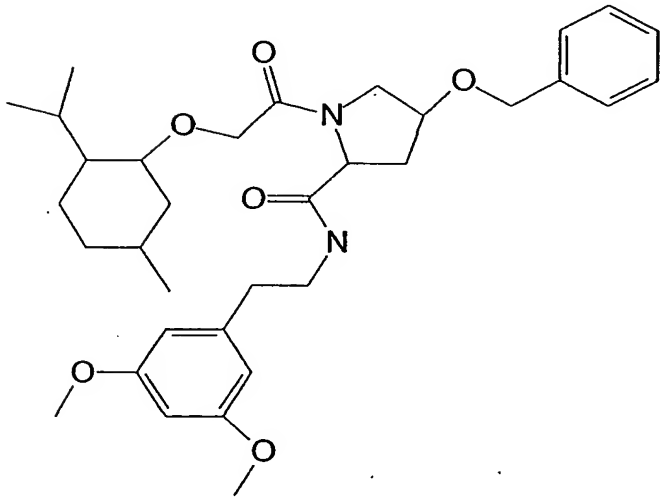


FIG. 288

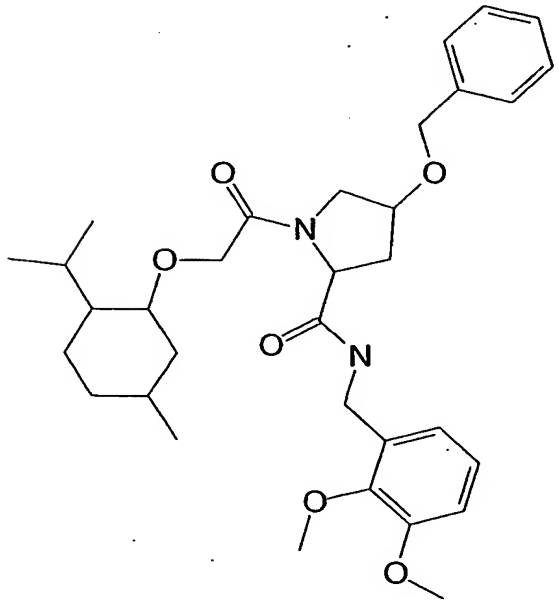


FIG. 289

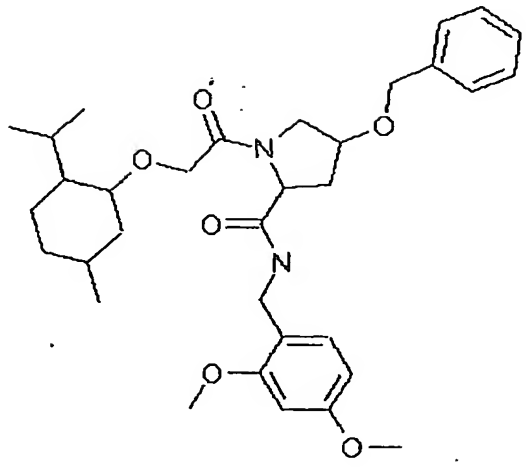
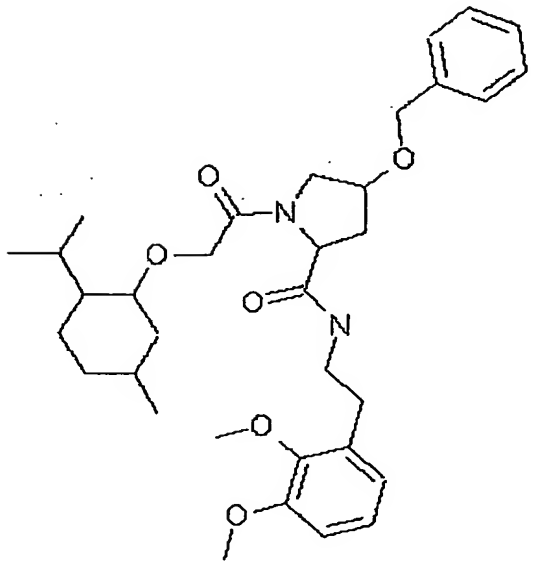


FIG. 290



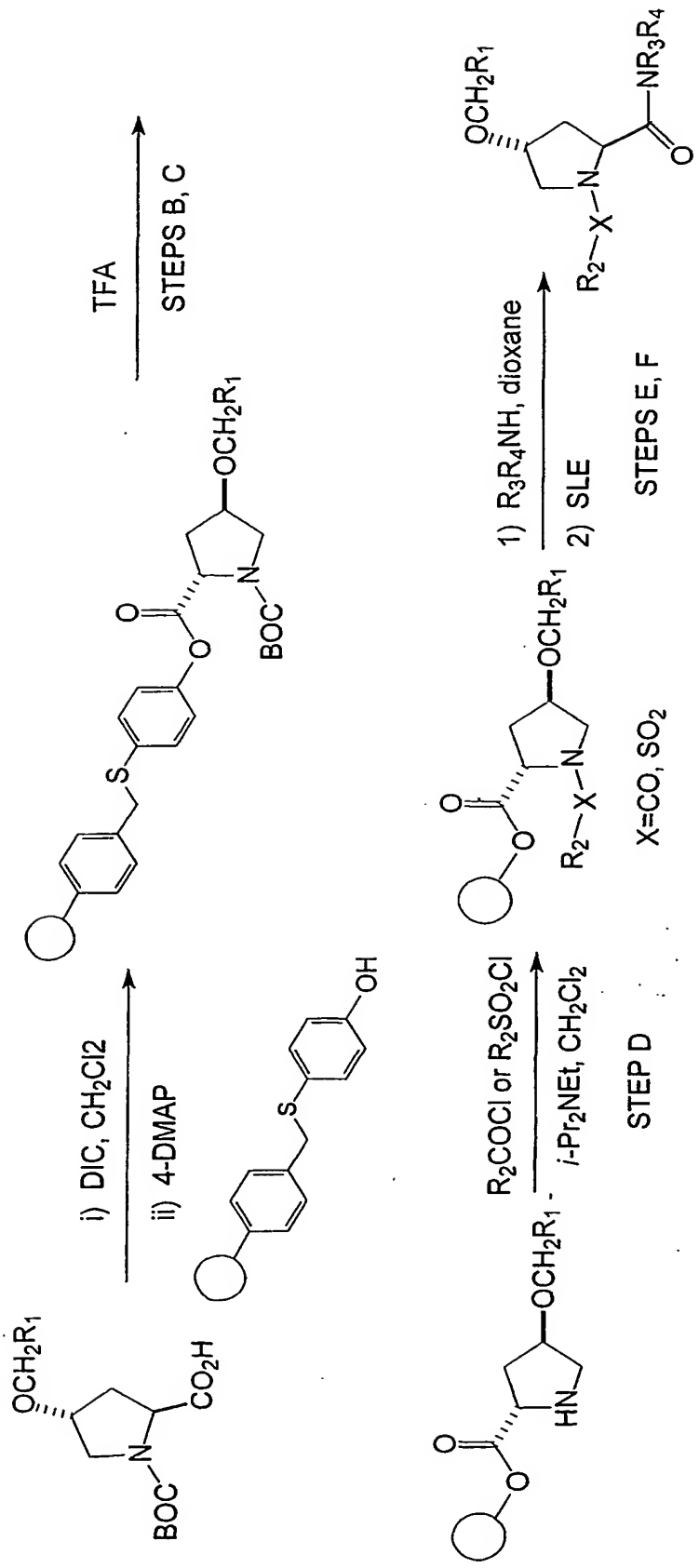


FIG. 291

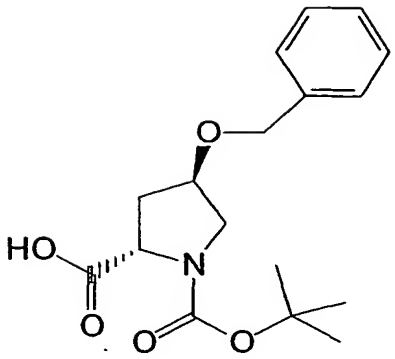


FIG. 292

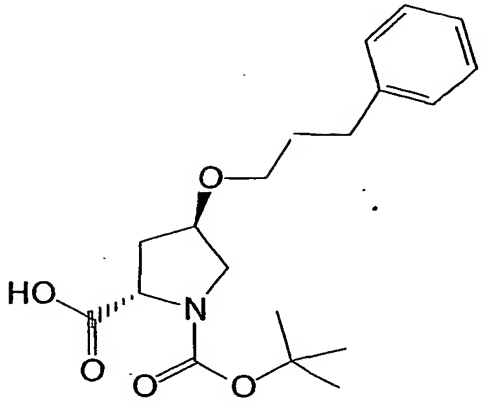


FIG. 293

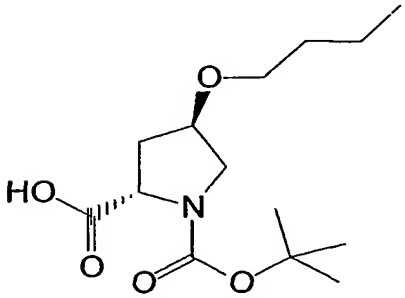


FIG. 294

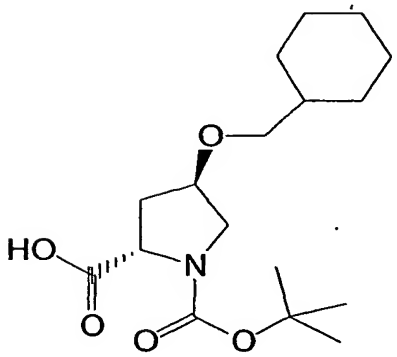


FIG. 295

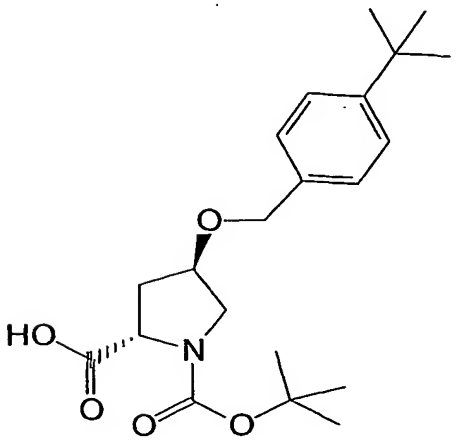


FIG. 296

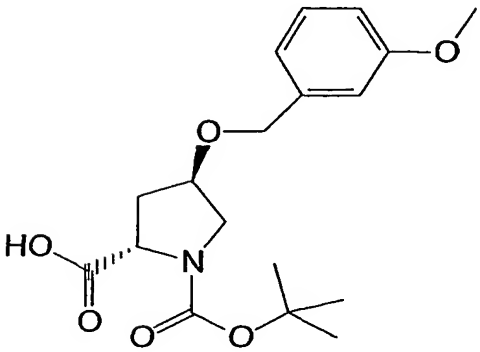


FIG. 297

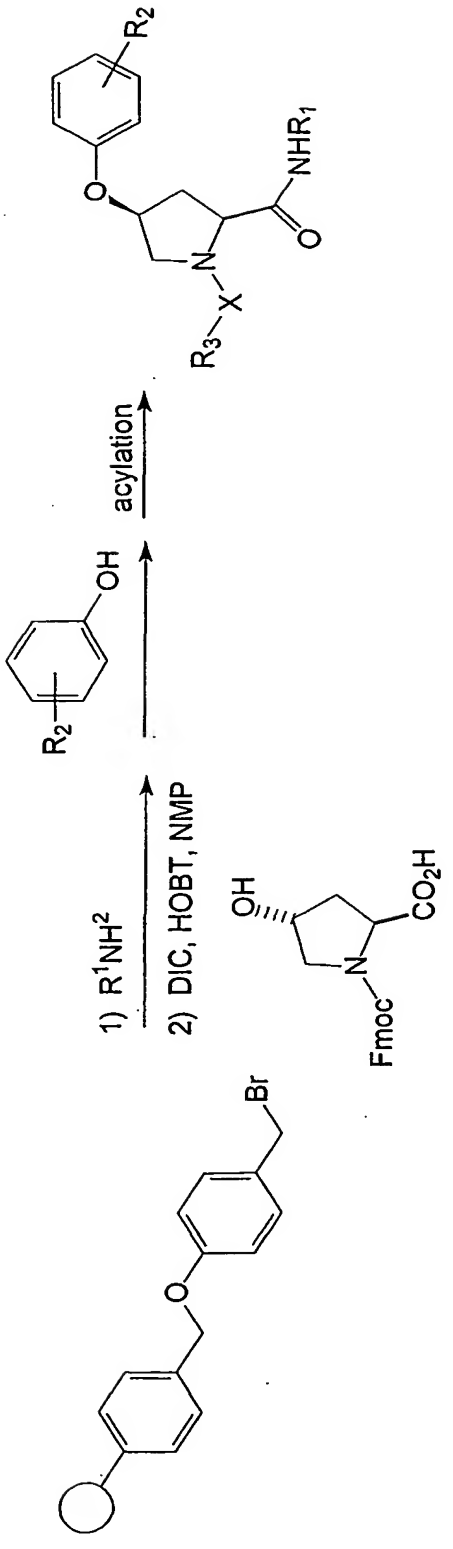


FIG. 298

FIG. 299

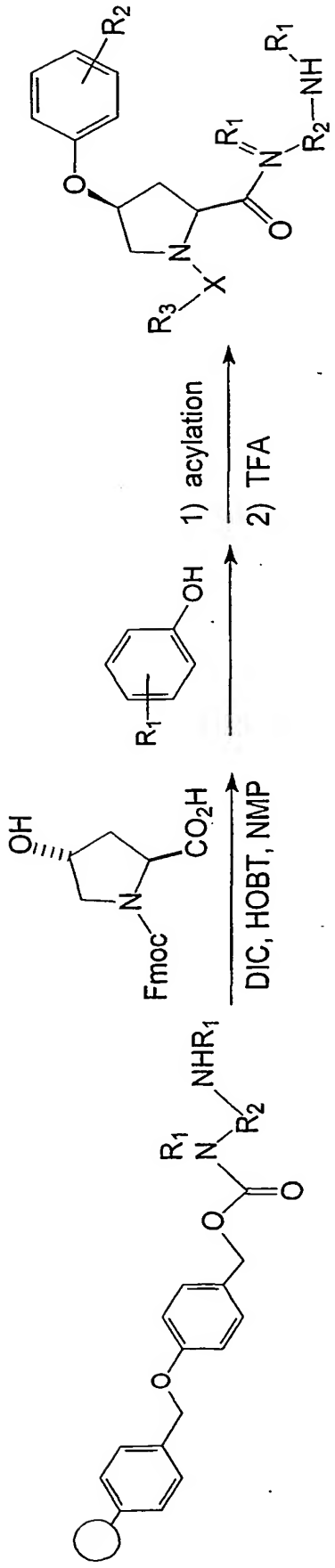


FIG. 300

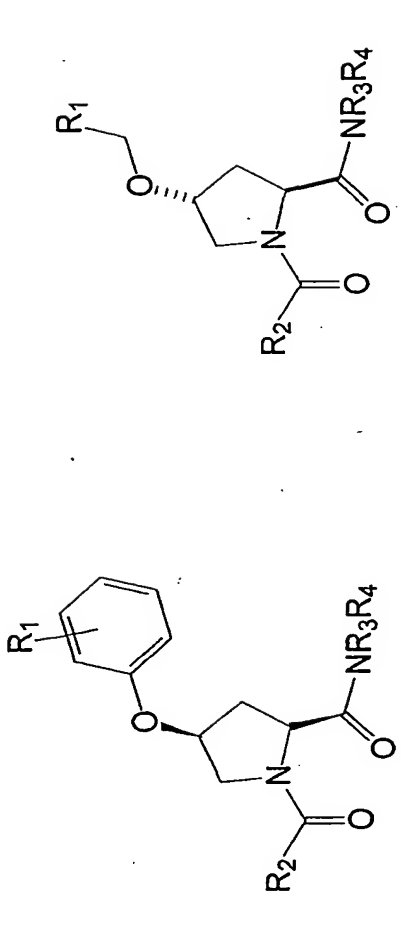


FIG. 301

INTERNATIONAL SEARCH REPORT

In ›nal Application No
PCT/US 01/02871

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N37/36 A01N41/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 171 355 A (BERTRAM HEINZ-JUERGEN ET AL) 15 December 1992 (1992-12-15) claims	1
A	WO 92 15555 A (MONSANTO CO) 17 September 1992 (1992-09-17) page 2, line 1 -page 4, line 19 compound 54 compound 125	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2001	16/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Donovan-Beermann, T

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INTERNATIONAL SEARCH REPORT

Int ıal Application No
PCT/US 01/02871

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1982 LIANG Y-Y ET AL: "AUTO RADIOGRAPHIC STUDY ON TISSUE LOCALIZATION OF CARBON-14 LABELED CUCURBITINE IN MICE" Database accession no. PREV198376062994 XP002164312 abstract & ACTA PHARMACOLOGICA SINICA, vol. 3, no. 4, 1982, pages 267-269, ISSN: 0253-9756 abstract	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]nal Application No
PCT/US 01/02871

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